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# Cardiovascular Update


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*UCL LONDON*

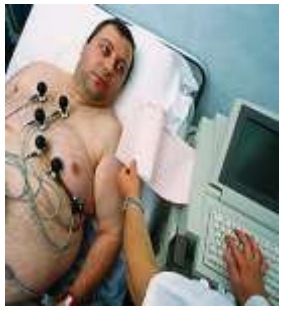
world class expertise local care

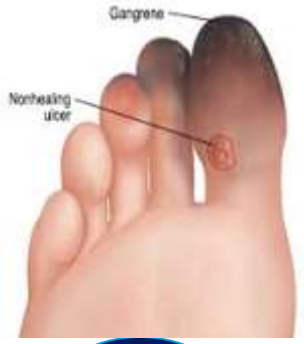
# Disclosures

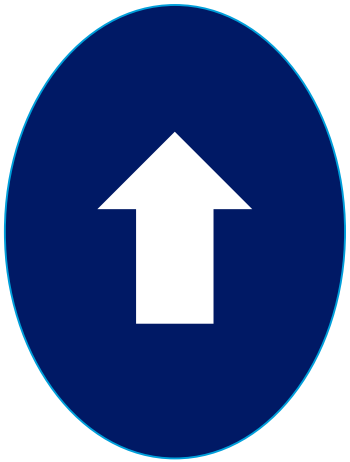
- Educational sponsorship, speaker or advisory related honoraria:
- AstraZenica, Boehringer Ingelheim, Janssen, Lilly, Napp, MSD, Novo Nordisk, Sanofi and Takeda

# CVD-related mortality increases in patients with T2D

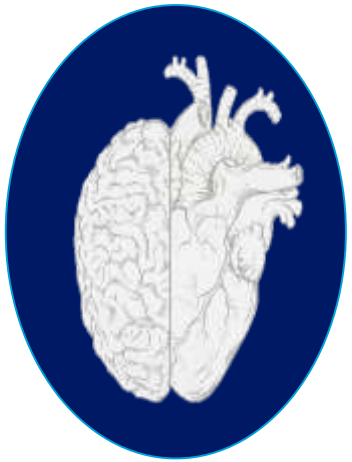
- People with T2D:





Have a **32%** greater chance of mortality than those without T2D[1]



Are **2x** as likely to have coronary heart disease or suffer a stroke as people who do not have diabetes[2]

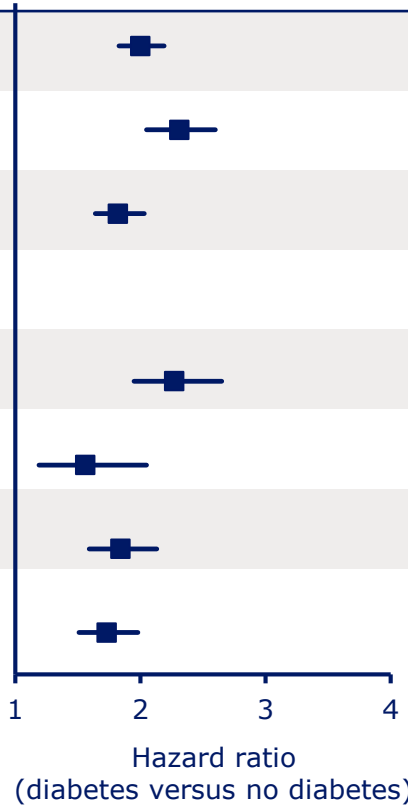
Are **10–20x** more likely to have a lower-limb amputation than people without diabetes[3]

- CVD, cardiovascular disease; T2D, type 2 diabetes
-

1. Diabetes UK. Facts and stats. Diabetes UK website; 2016. https://diabetes-resources-production.s3-eu-west-1.amazonaws.com/diabetes-storage/migration/pdf/DiabetesUK_Facts_Stats_Oct16.pdf [Accessed Dec 2017]; 2. Emerging Risk Factors Collaboration. Lancet 2010;375: 2215–22; 3. World Health Organization. Global report on diabetes. WHO website; 2016. http://www.who.int/diabetes/global-report/en/ [Accessed Nov 2017]

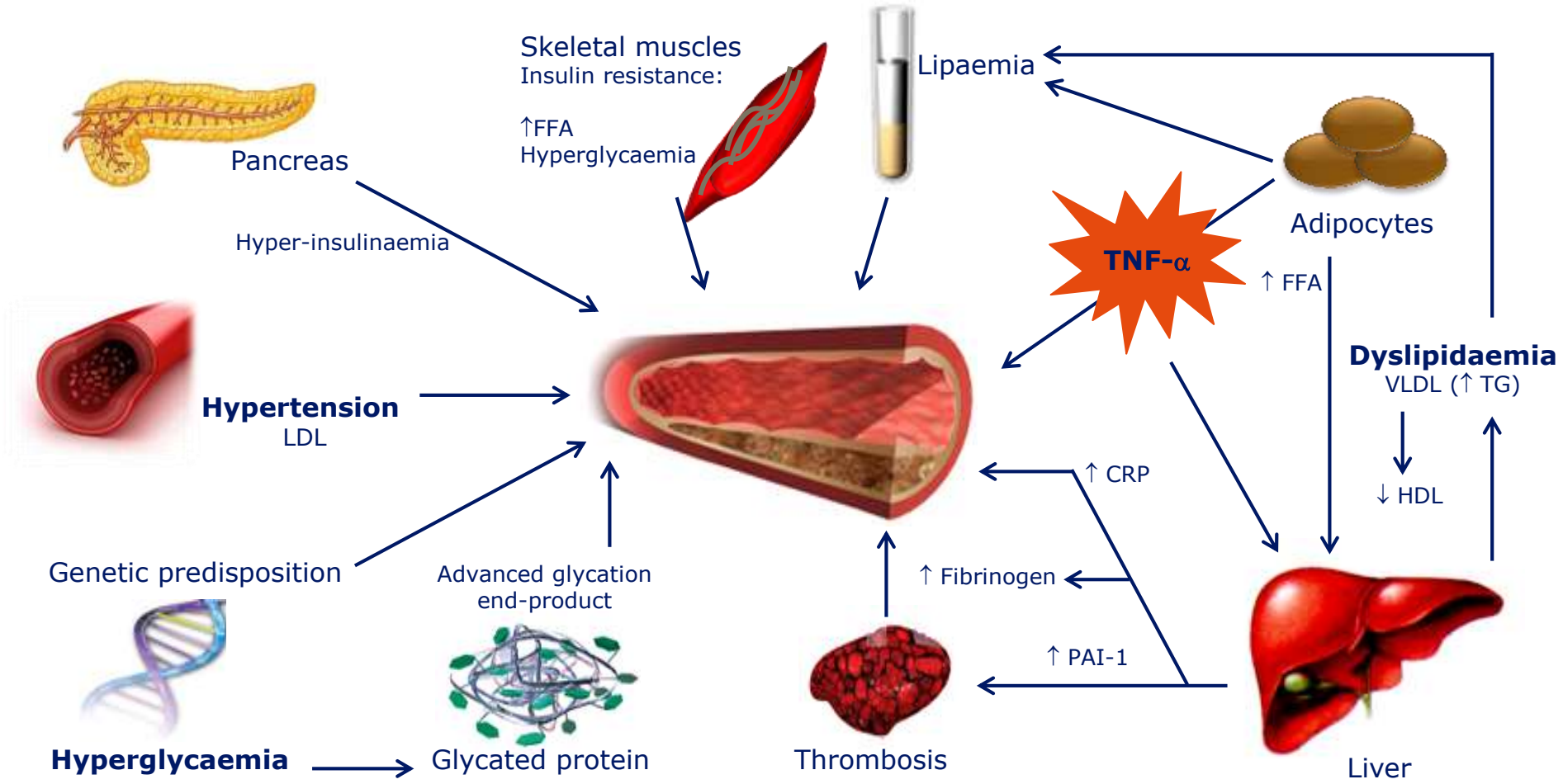
# Diabetes doubles the risk of vascular disease

| | Number of cases | Hazard ratio | 95% CI |
|---|---|---|---|
| **Coronary heart disease*** | 26,505 | 2.00 | 1.83; 2.19 |
| Coronary death | 11,556 | 2.31 | 2.05; 2.60 |
| Non-fatal MI | 14,741 | 1.82 | 1.64; 2.03 |
| **Stroke subtypes*** | | | |
| Ischaemic stroke | 3,799 | 2.27 | 1.95; 2.65 |
| Haemorrhagic stroke | 1,183 | 1.56 | 1.19; 2.05 |
| Unclassified stroke | 4,973 | 1.84 | 1.59; 2.13 |
| **Other vascular deaths** | 3,826 | 1.73 | 1.51; 1.98 |




- Analyses were based on 530,083 participants. Hazard ratios adjusted for age, smoking status, body mass index, and systolic blood pressure, and, where appropriate, stratified by sex and trial arm; 208 coronary heart disease outcomes that contributed to the grand total could not contribute to the subtotals of coronary death or non-fatal MI because there were <11 cases of these coronary disease subtypes in some studies. *Includes both fatal and non-fatal events. CI, confidence interval; MI, myocardial infarction
- Adapted from Emerging Risk Factors Collaboration; *Lancet* 2010; 375:2215–22

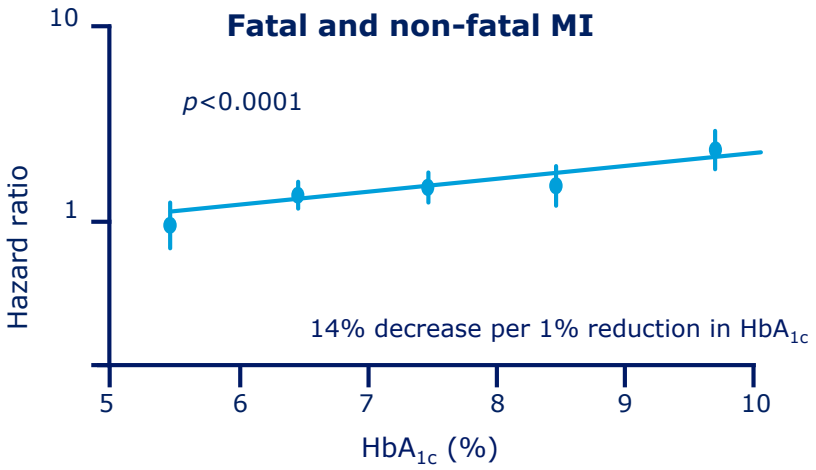
# Many factors contribute to increased CV risk in T2D

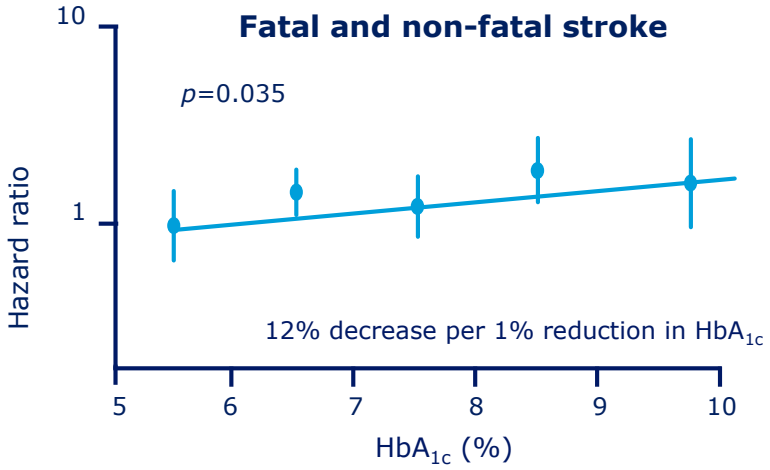


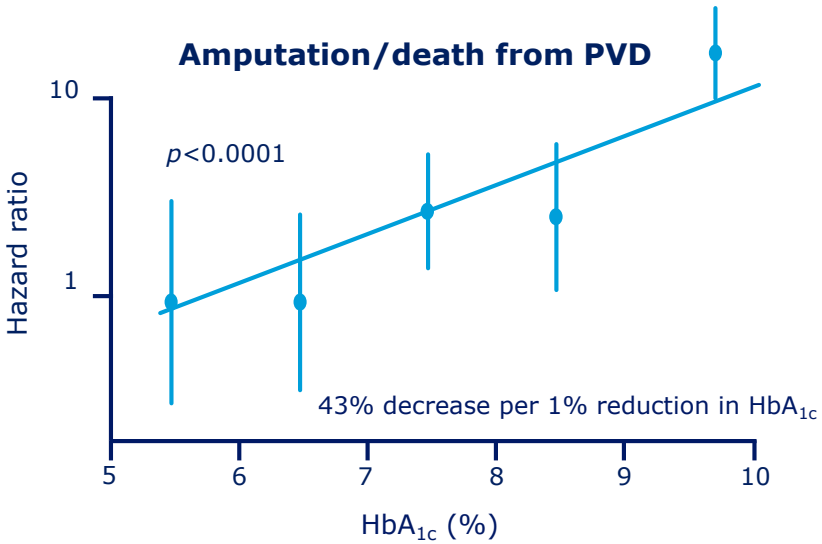

CRP, C-reactive peptide; CV, cardiovascular; FFA, free fatty acid; HDL, high-density lipoprotein; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; PAI-1, plasminogen activator inhibitor-1; T2D, type 2 diabetes; TG, triglyceride; TNF-α, tumour necrosis factor-α; VLDL, very low-density lipoprotein
Adapted from Libby, Plutzky. *Circulation* 2002;106:2760–63

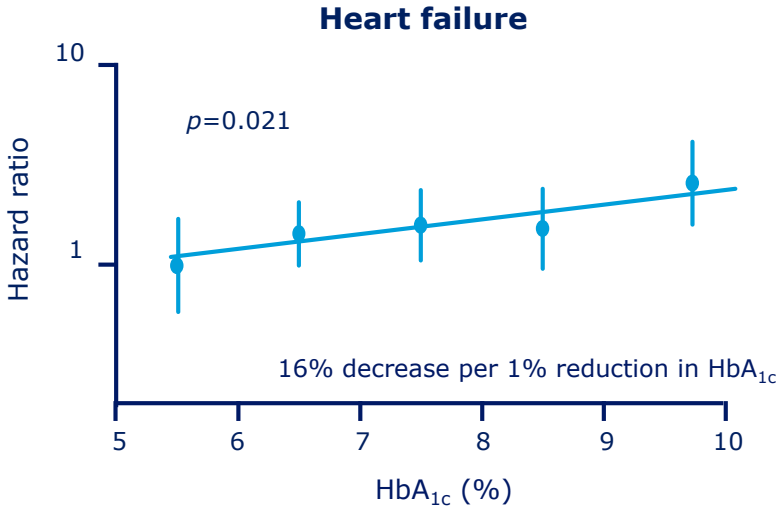
# The role of glycaemic control in the context of cardiovascular risk

# Higher $HbA_{1c}$ predicts higher CV risk



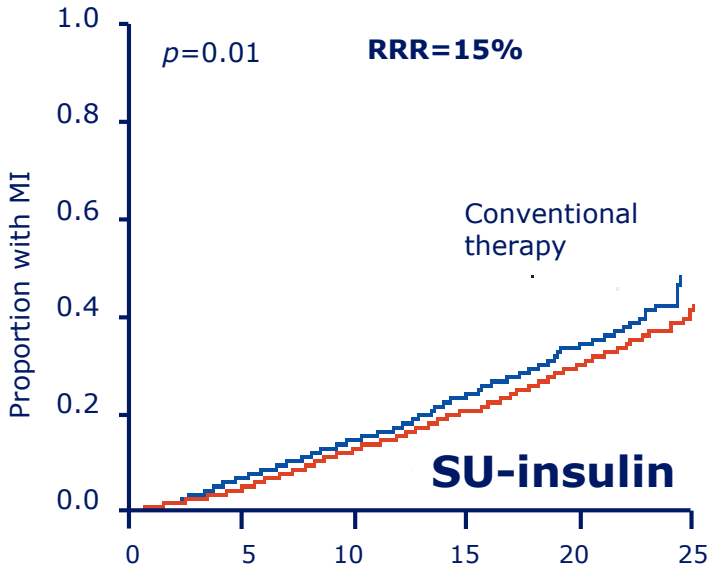



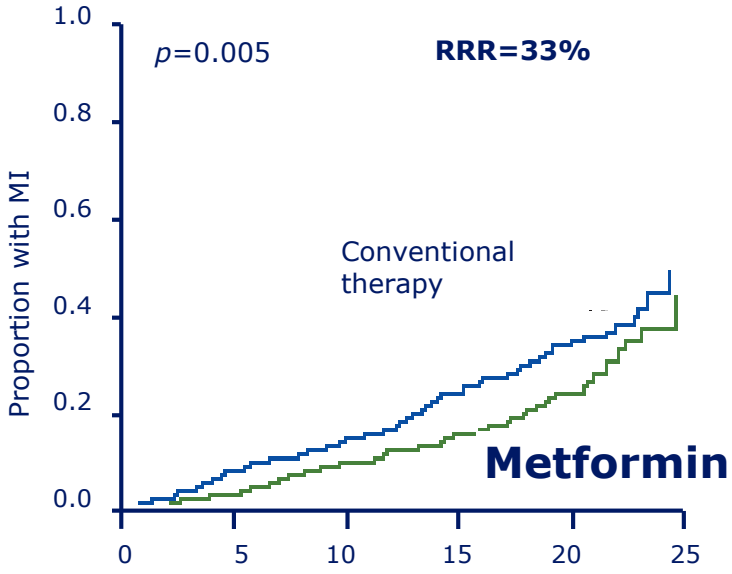

Reference category (hazard ratio 1.0) is $HbA_{1c}$ <6% with log linear scales. CV, cardiovascular; $HbA_{1c}$, glycosylated haemoglobin; MI, myocardial infarction; PVD, peripheral vascular disease

Adapted from Stratton *et al. BMJ* 2000;321:405–12

# CV benefits of initial tight glycaemic control – 10 years of follow-up

## UKPDS (1998)



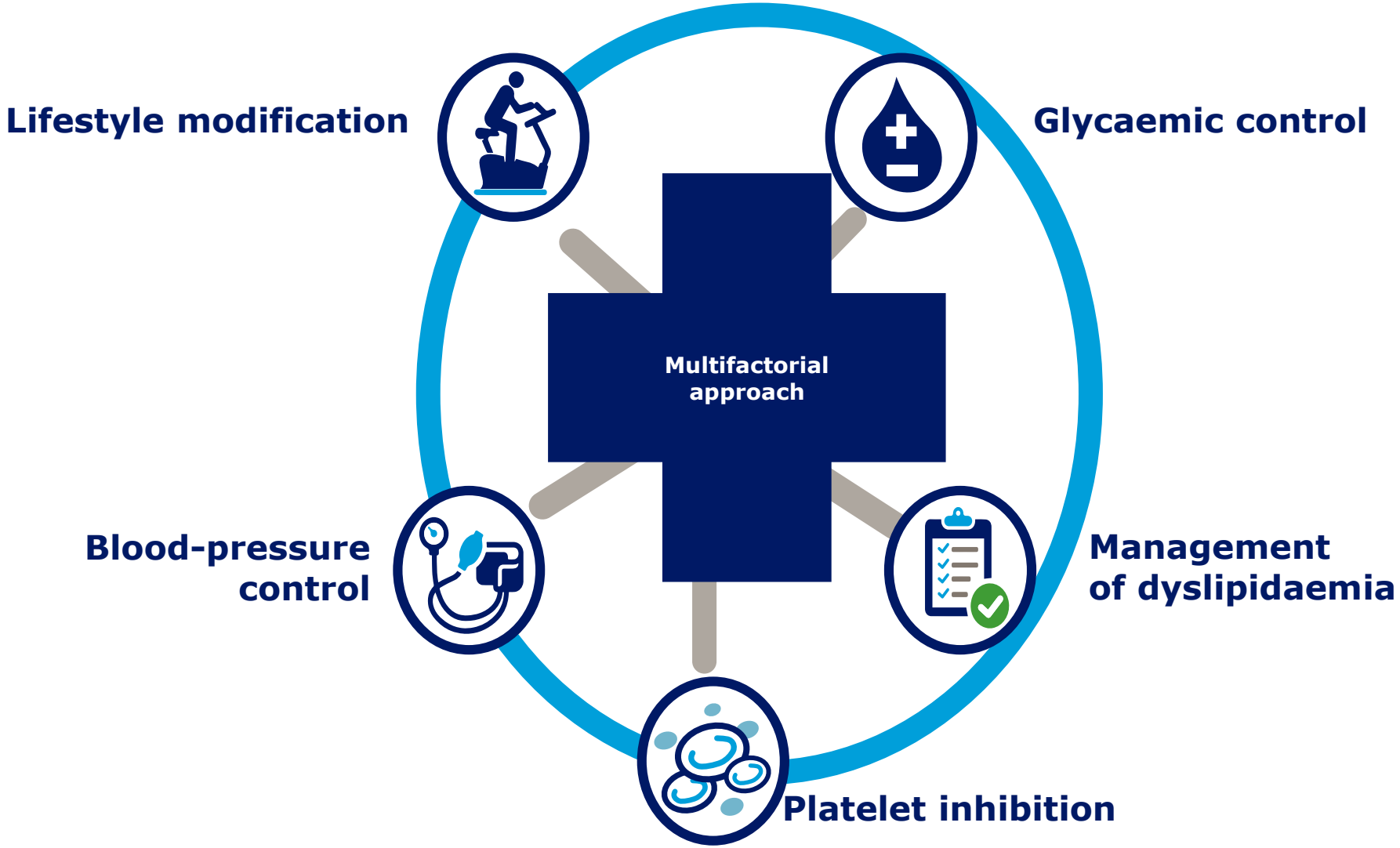

Years since randomisation

| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| Conventional: | 1138 | 1013 | 857 | 578 | 221 | 20 |
| SU/insulin: | 2729 | 2488 | 2097 | 1459 | 577 | 66 |

| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| Conventional: | 411 | 360 | 311 | 213 | 95 | 4 |
| Metformin: | 342 | 317 | 274 | 214 | 106 | 16 |

Patients randomised to conventional glucose control (diet) or intensive glucose control (SU or insulin, or metformin if >120% of ideal body weight)
CV, cardiovascular; MI, myocardial infarction; RRR, relative risk reduction; SU, sulphonylurea; UKPDS, UK Prospective Diabetes Study.
Adapted from Holman *et al. N Engl J Med* 2008;359:1577–89

# How do we currently modify CV risk in T2D?



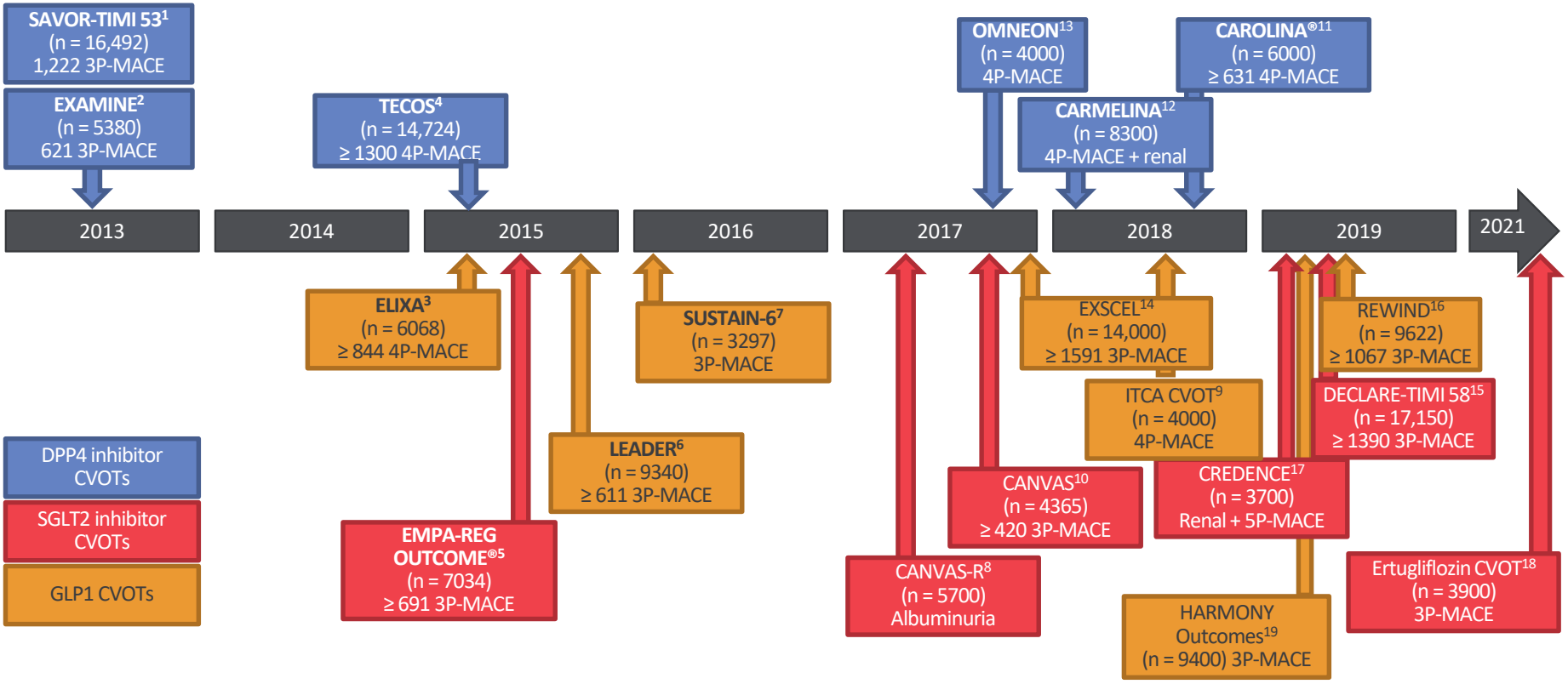

CV, cardiovascular; T2D, type 2 diabetes

1. Rydén *et al. Eur Heart J* 2013;34:3035–87; 2. Fox *et al. Diabetes Care* 2015;38:1777–803; 3. Piepoli *et al. Eur Heart J* 2016;37:2315–81

# Cardiovascular outcome trials (CVOTs) in patients with type 2 diabetes

## Background

# CV safety trials are being conducted for each compound within the newer classes




Timings represent estimated completion dates as per ClinicalTrials.gov.

Adapted from Johansen. World J Diabetes 2015;6:1092–96. (references 1–19 expanded in slide notes)



ACROSS T2D

# HARMONY –CVOT -Albiglutide

- **The Lancet:** www.thelancet.com

## Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial

*Adrian F Hernandez, Jennifer B Green, Salim Janmohamed, Ralph B D'Agostino Sr, Christopher B Granger, Nigel P Jones, Lawrence A Leiter, Anne E Rosenberg, Kristina N Sigmon, Matthew C Somerville, Karl M Thorpe, John J V McMurray, Stefano Del Prato, for the Harmony Outcomes committees and investigators**

www.thelancet.com Published online October 2, 2018 http://dx.doi.org/10.1016/S0140-6736(18)32261-X

Harmony
Outcomes

# Baseline Characteristics

| | Albiglutide n=4,731 | Placebo n=4,732 |
|---|---|---|
| Age (years) | 64 ± 9 | 64 ± 9 |
| Men (%) | 70 | 69 |
| White (%) | 70 | 69 |
| Duration of diabetes (years) | 14 ± 9 | 14 ± 9 |
| $HbA_{1c}$ (%) | 8.8 ± 1.5 | 8.7 ± 1.5 |
| Body mass index ($kg/m^2$) | 32 ± 6 | 32 ± 6 |
| SBP (mmHg) | 135 ± 17 | 135 ± 17 |
| DBP (mmHg) | 77 ± 10 | 77 ± 10 |
| eGFR ($mL/min/1.73\ m^2$) | 79 ± 26 | 79 ± 25 |
| eGFR <60 $mL/min/1.73\ m^2$ (%) | 23 | 24 |

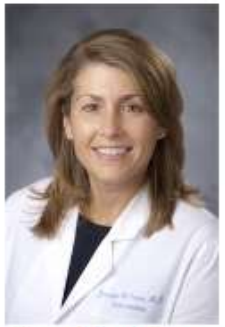
*Mean ± SD. eGFR calculated by **M**odification of **D**iet in **R**enal **D**isease formula.*
*DBP, diastolic blood pressure; SBP, systolic blood pressure*

# Cardiovascular History at Baseline

| % | Albiglutide n=4,731 | Placebo n=4,732 |
|---|---|---|
| Coronary artery disease* | 70 | 71 |
| Myocardial Infarction | 47 | 47 |
| Coronary Artery Bypass Graft | 19 | 18 |
| Percutaneous Coronary Intervention | 43 | 45 |
| Stroke | 17 | 18 |
| Peripheral arterial disease | 25 | 24 |
| Heart failure | 20 | 20 |
| Hypertension | 86 | 86 |
| Current smoker | 16 | 16 |

*Any of MI, coronary artery bypass grafting, percutaneous coronary intervention or ≥50% stenosis of coronary artery on angiography





Jennifer Green

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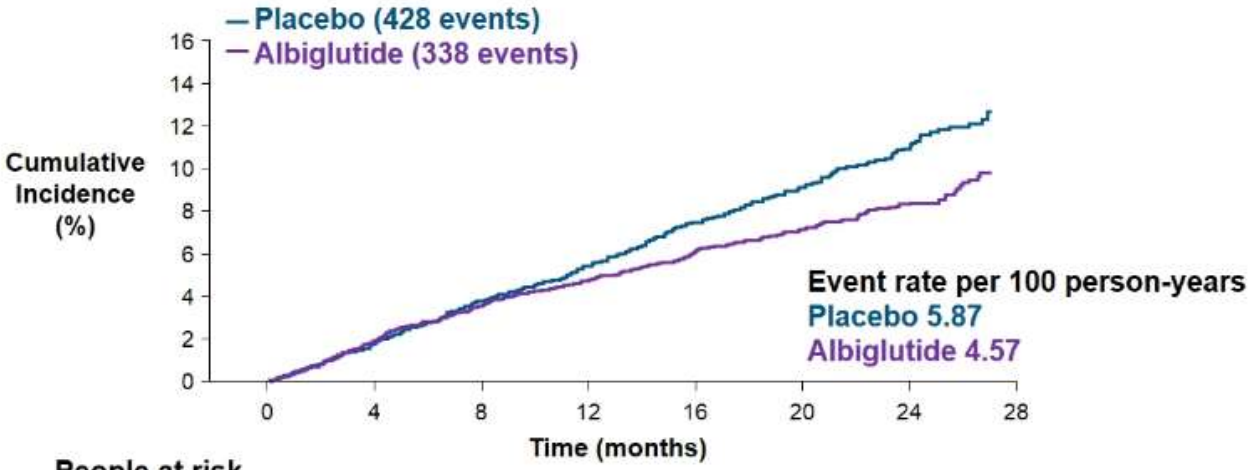
# Anti-hyperglycaemic Medications at Baseline

| % | Albiglutide n=4,731 | Placebo n=4,732 |
|---|---|---|
| Diet alone | <1 | <1 |
| Metformin | 73 | 74 |
| Sulfonylurea | 28 | 29 |
| DPP-4 inhibitor | 15 | 16 |
| SGLT-2 inhibitor | 7 | 6 |
| Thiazolidinedione | 2 | 2 |
| Glinide | 1 | 2 |
| Insulin | 60 | 58 |

*SGLT-2, sodium-glucose cotransporter-2*

# Primary Outcome:
# Time to CV Death, MI or Stroke (MACE)




Harmony Outcomes 51

John McMurray

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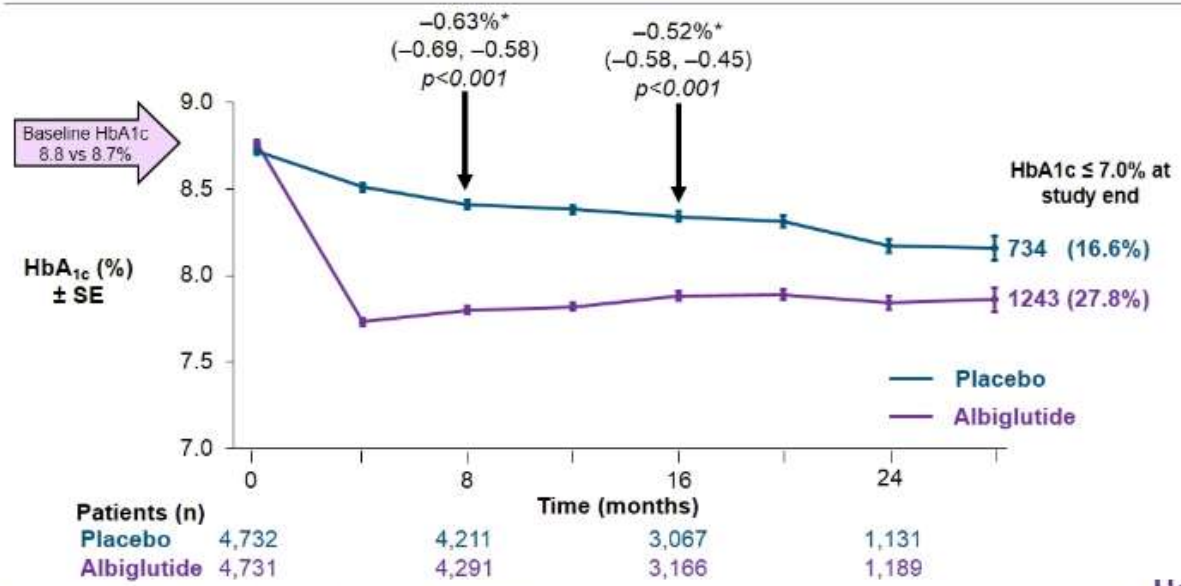
Hazard ratio 0.78 (0.61-0.9)
p=0.0006 superiority

# Secondary Endpoints and All-Cause Death

| | Albiglutide (n=4,731) | Placebo (n=4,732) | HR (95% CI) | p-value |
|---|---|---|---|---|
| MACE (primary) | 338 | 428 | 0.78 (0.68, 0.90) | <0.001 |
| MACE or urg. revasc. | 373 | 468 | 0.78 (0.69, 0.90) | <0.001 |
| Cardiovascular death | 122 | 130 | 0.93 (0.73, 1.19) | 0.578 |
| Myocardial infarction* | 181 | 240 | 0.75 (0.61, 0.90) | 0.003 |
| Stroke* | 94 | 108 | 0.86 (0.66, 1.14) | 0.300 |
| CV death or HF hosp. | 188 | 218 | 0.85 (0.70, 1.04) | 0.113 |
| All-cause death | 196 | 205 | 0.95 (0.79, 1.16) | 0.644 |

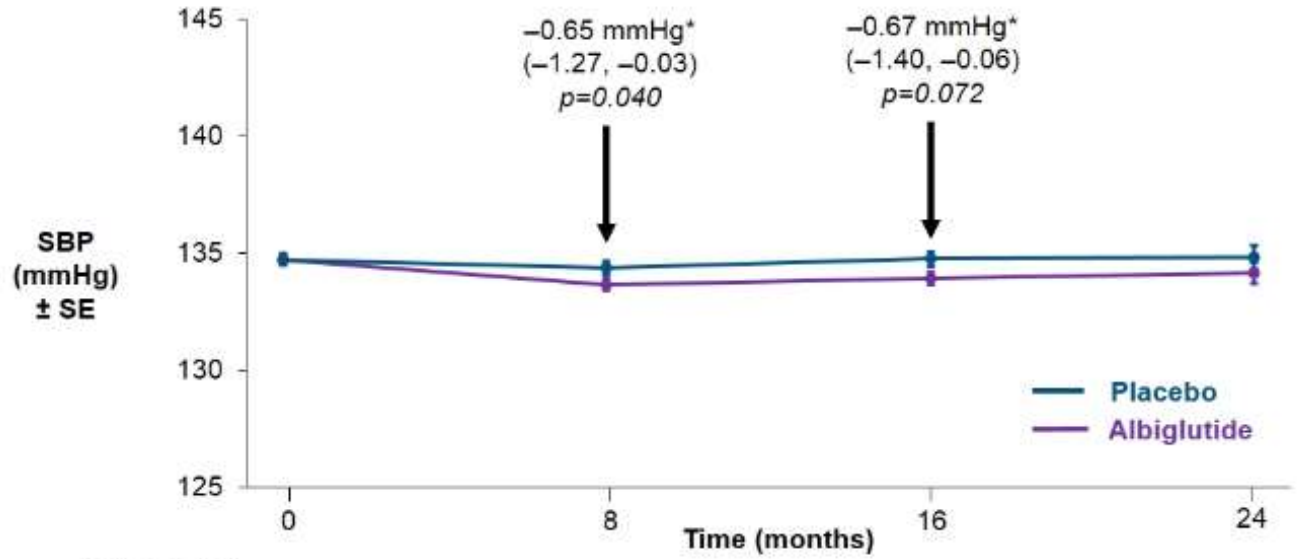
*Fatal and non-fatal; HF hosp, hospitalisation for heart failure*
*MACE or urg. revasc., Major adverse cardiovascular event or urgent revascularisation for unstable angina*

# Mean $HbA_{1c}$ Over Time




*albiglutide vs. placebo, difference in change from baseline (95% CI) by mixed model repeated measurements comparisons Assessments shown at pre-specified timepoints. SE, standard error

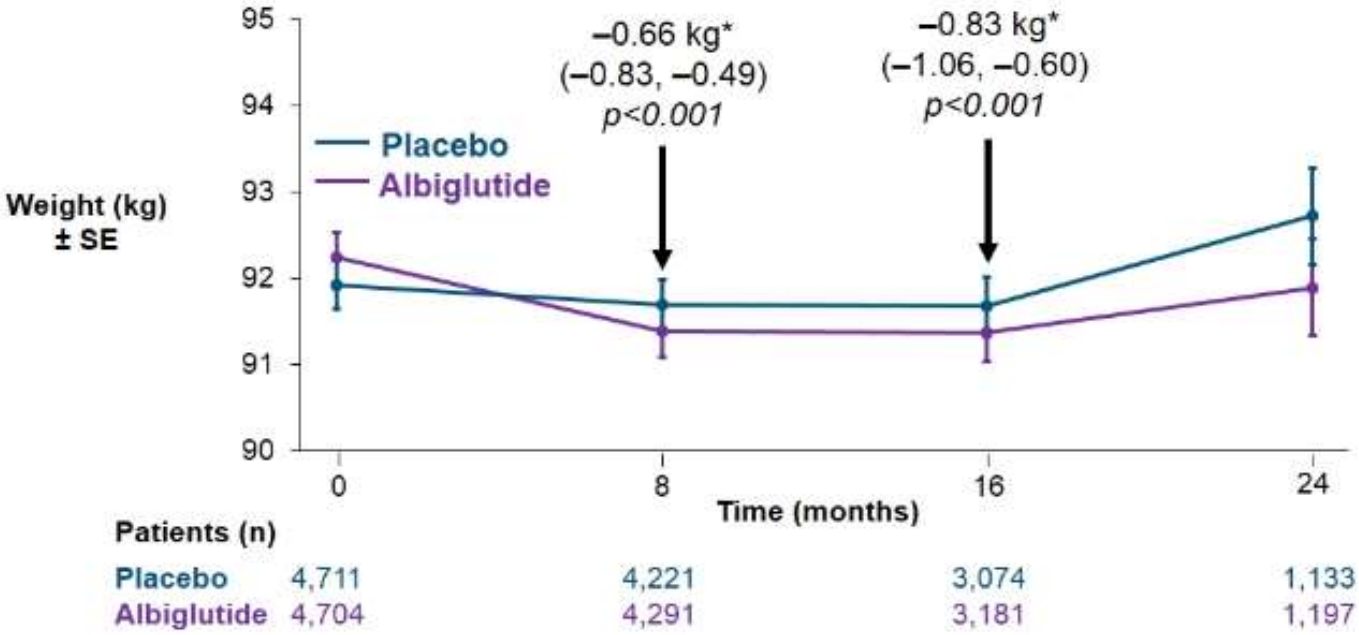
# Systolic Blood Pressure Over Time




| Patients (n) | | | | |
|---|---|---|---|---|
| Placebo | 4,721 | 4,249 | 3,088 | 1,137 |
| Albiglutide | 4,715 | 4,326 | 3,195 | 1,200 |

*albiglutide vs. placebo, difference in change from baseline (95% CI) by mixed model repeated measurements comparisons

# Mean Body Weight Over Time




| Patients (n) | | | | |
|---|---|---|---|---|
| Placebo | 4,711 | 4,221 | 3,074 | 1,133 |
| Albiglutide | 4,704 | 4,291 | 3,181 | 1,197 |

*albiglutide vs. placebo, difference in change from baseline (95% CI) by mixed model repeated measurements comparisons Assessments shown at pre-specified timepoints

# Harmony GLP-1 CVOT trial (Albiglutide)

- ~60 fewer MI events in median time only 1.6 yr in v. high risk population
- NNT 50 for 1.6 yr
- But…little effect on :
  - Weight -0.83kg
  - BP -0.67mmHg
  - Hba1c -0.5%

*Are there pleiomorphic effects of GLP-1-R agonist……??*

# Differences Among Trials That May Have Influenced Outcomes

| | ELIXA N=6,068 | LEADER N=9,340 | SUSTAIN-6 N=3,297 | EXSCEL N=14,752 | Harmony Outcomes N=9,463 |
|---|---|---|---|---|---|
| Agent | Lixisenatide | Liraglutide | Semaglutide | Exenatide XR | Albiglutide |
| Dose strategy | Increased if tolerated | Forced increase | Forced increase | Single dose | Clinical titration |
| Baseline mean $HbA_{1c}$ (%) | 7.7 ± 1.3 | 8.7 ± 1.6 | 8.7 ± 1.5 | 8.1 ± 1.0 | 8.7 ± 1.5 |
| Established CV disease (%) | 100 | 81 | 83 | 73 | 100 |
| First MACE (n) | 805 | 1302 | 254 | 1744 | 766 |
| Median follow-up duration (y) | 2.1 | 3.8 | 2.1 | 3.2 | 1.6 |
| DPP-4 inhibitor | × | × | × | ✓ | ✓ |

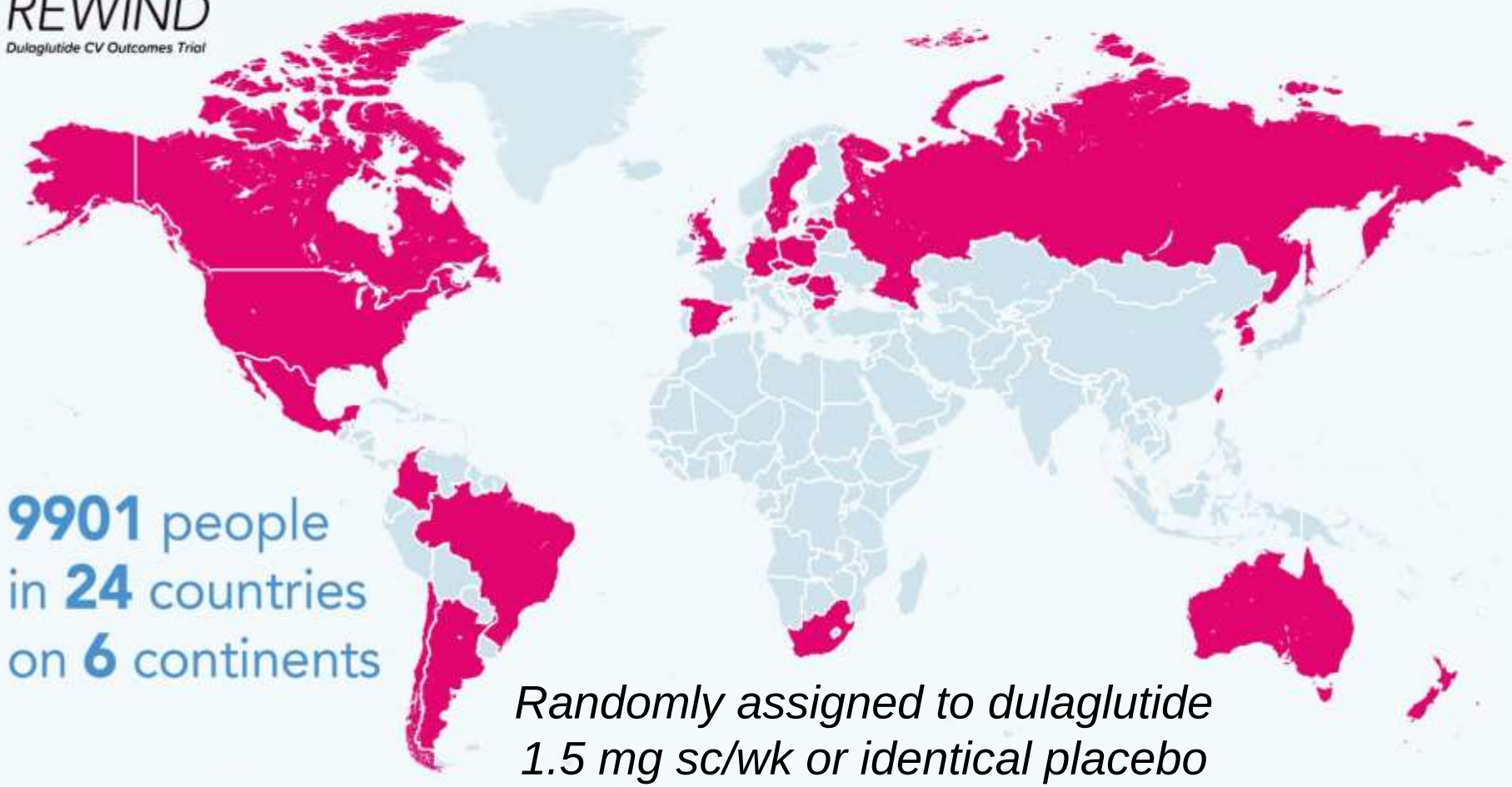
Harmony Outcomes


**R**esearching CV **E**vents with a **W**eekly **IN**cretin in **D**iabetes

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Recruitment at 371 sites from Aug 2011-Aug 2013

REWIND
Dulaglutide CV Outcomes Trial




*Randomly assigned to dulaglutide 1.5 mg sc/wk or identical placebo*

REWIND
Dulaglutide CV Outcomes Trial

# Diabetes-related Characteristics

| | **All Participants N=9901** | Dulaglutide N=4949 | Placebo N=4952 |
|---|---|---|---|
| **HbA1c (%)** | **7.3** | 7.3 | 7.4 |
| **DM Duration (y)** | **10.5** | 10.5 | 10.6 |
| **Retinopathy (%)** | **9.0** | 9.1 | 8.9 |
| **eGFR <60 ml/min/1.73m$^2$ (%)** | **22.2** | 21.8 | 22.6 |
| **Albuminuria (%)*** | **35.0** | 34.5 | 35.5 |
| **Metformin (%)** | **81.2** | 81.3 | 81.1 |
| **Sulfonylurea (%)** | **46.0** | 45.9 | 46.1 |
| **Insulin (%)** | **23.9** | 24.0 | 23.7 |
| **DPP4i (%)** | **5.7** | 5.4 | 6.0 |
| **Thiazolidinedione (%)** | **1.7** | 2.0 | 1.4 |
| **Other incl. SGLT2i (%)** | **0.3** | 0.3 | 0.4 |

**** ACR ≥ 3.39 mg/mmol or 30 mg/g***

REWIND
Dulaglutide CV Outcomes Trial

# Baseline Measures – SI Units

| | **All Participants N=9901** | Dulaglutide N=4949 | Placebo N=4952 |
|---|---|---|---|
| **BMI (kg/m$^2$)** | **32.3** | 32.3 | 32.3 |
| **Systolic BP (mm Hg)** | **137.2** | 137.1 | 137.3 |
| **Diastolic BP (mm Hg)** | **78.5** | 78.4 | 78.5 |
| **Heart Rate (bpm)** | **71.5** | 71.4 | 71.6 |
| **Serum Creat (umol/l)** | **84.1** | 83.7 | 84.5 |
| **Median eGFR (ml/min/1.73m$^2$)** | **74.9** | 75.3 | 74.7 |
| **Median ACR (mg/mmol)** | **1.82** | 1.80 | 1.88 |
| **Cholesterol (mmol/L)** | **4.52** | 4.52 | 4.52 |
| **LDL (mmol/L)** | **2.56** | 2.56 | 2.56 |
| **HDL (mmol/L)** | **1.18** | 1.18 | 1.18 |
| **Median Triglycerides (mmol/L)** | **1.60** | 1.60 | 1.60 |

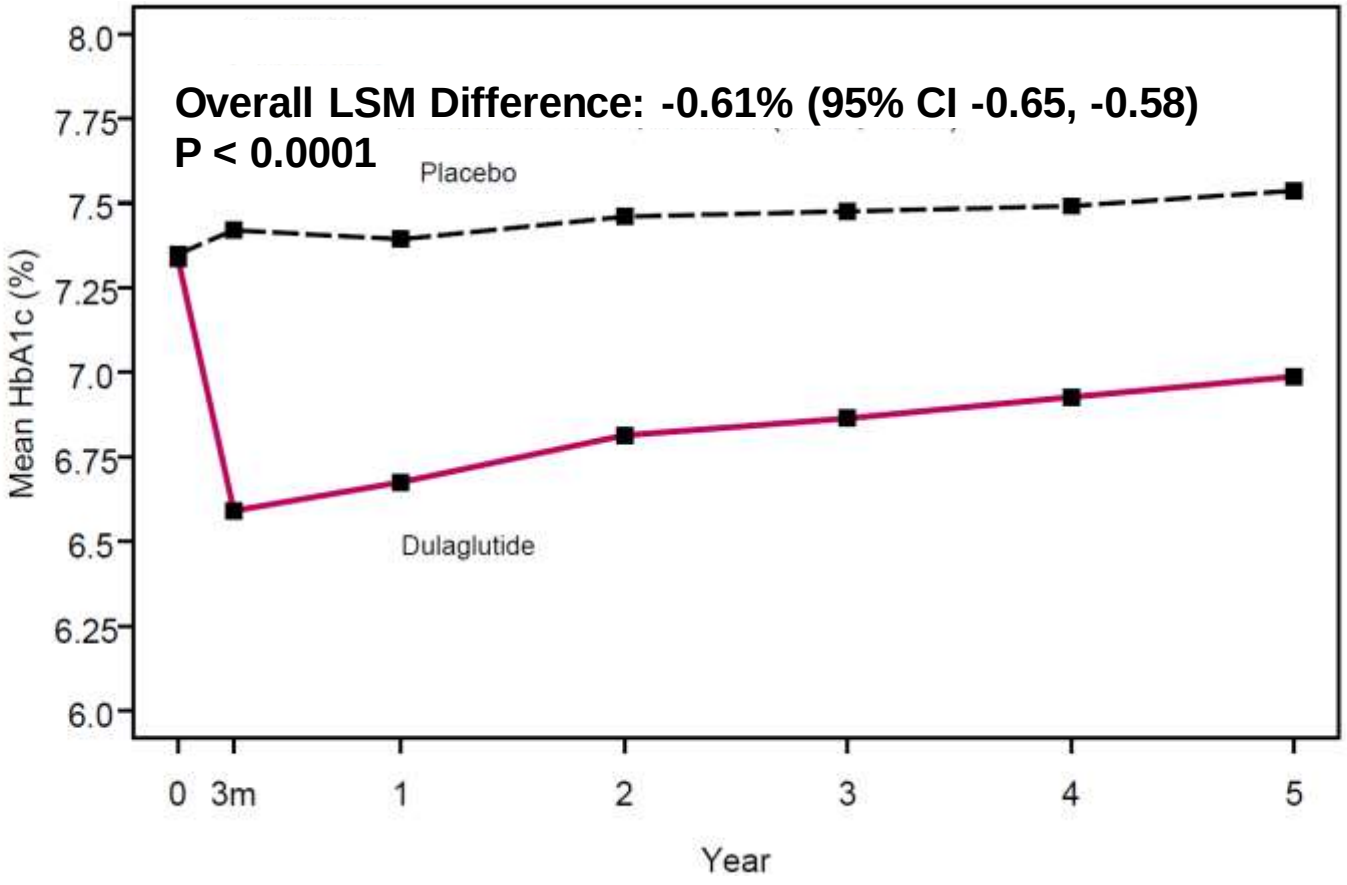
REWIND
Dulaglutide CV Outcomes Trial

# Baseline use of CV Drugs

| | **All Participants N=9901** | Dulaglutide N=4949 | Placebo N=4952 |
|---|---|---|---|
| **ACE/ARB (%)** | **81.5** | 81.0 | 82.0 |
| **Beta Blocker (%)** | **45.6** | 45.2 | 45.9 |
| **Other Blood Pressure (%)** | **56.6** | 55.9 | 57.2 |
| **Statin (%)** | **66.1** | 66.3 | 66.0 |
| **Fibrate (%)** | **9.1** | 9.1 | 9.0 |
| **Antiplatelet (%)** | **54.0** | 53.8 | 54.1 |

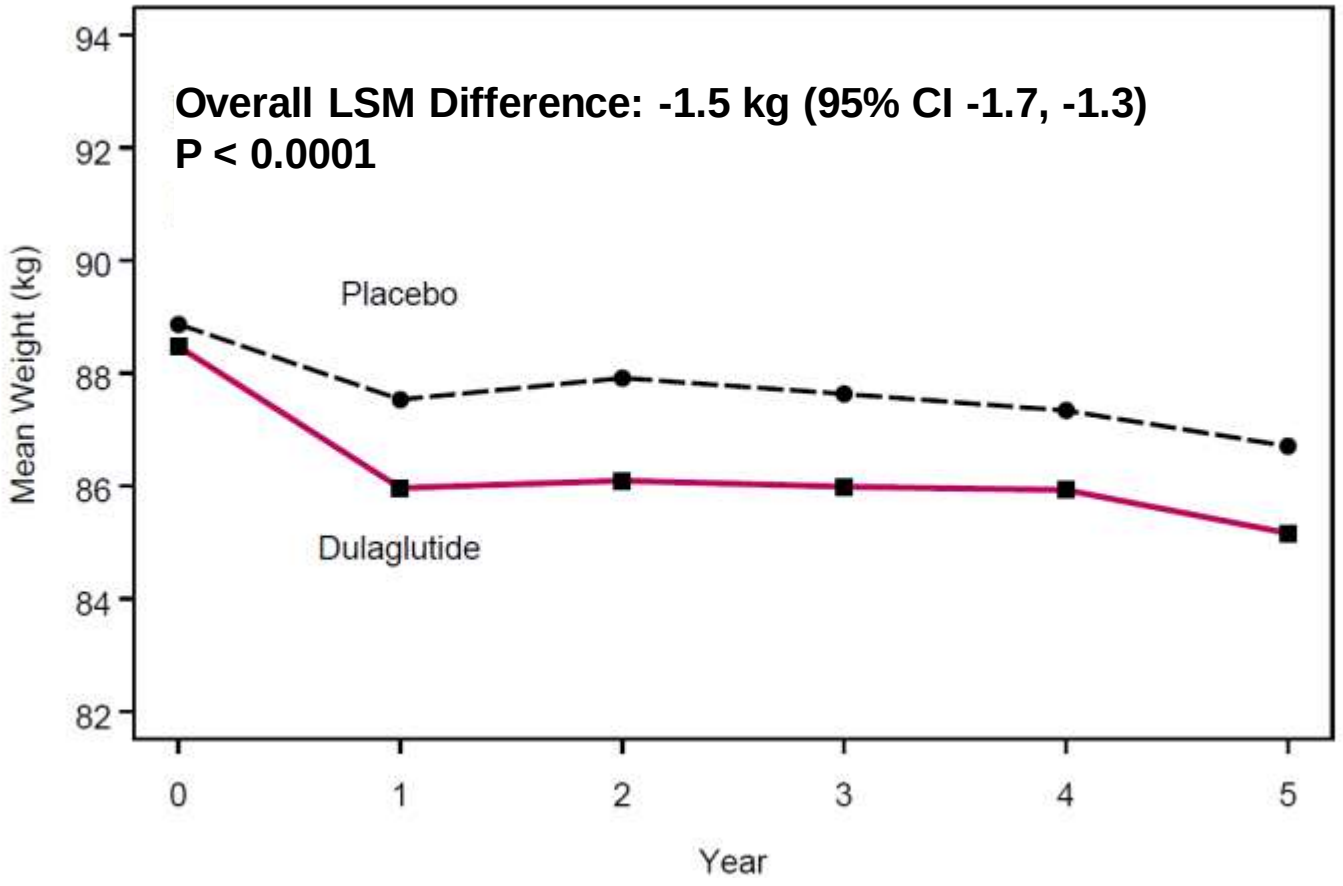
REWIND
Dulaglutide CV Outcomes Trial

# Dulaglutide's Effect on HbA1c



REWIND
Dulaglutide CV Outcomes Trial

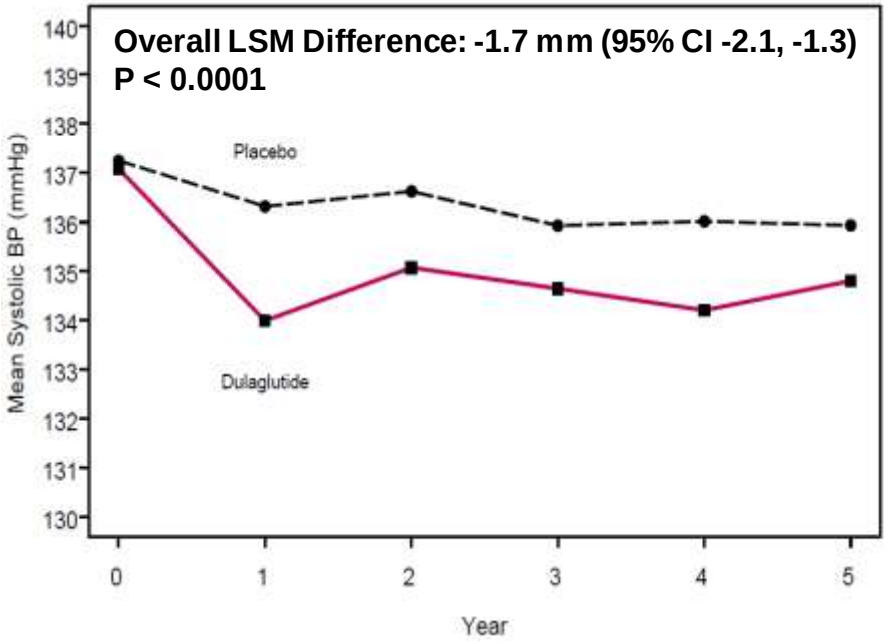
# Dulaglutide's Effect on Weight



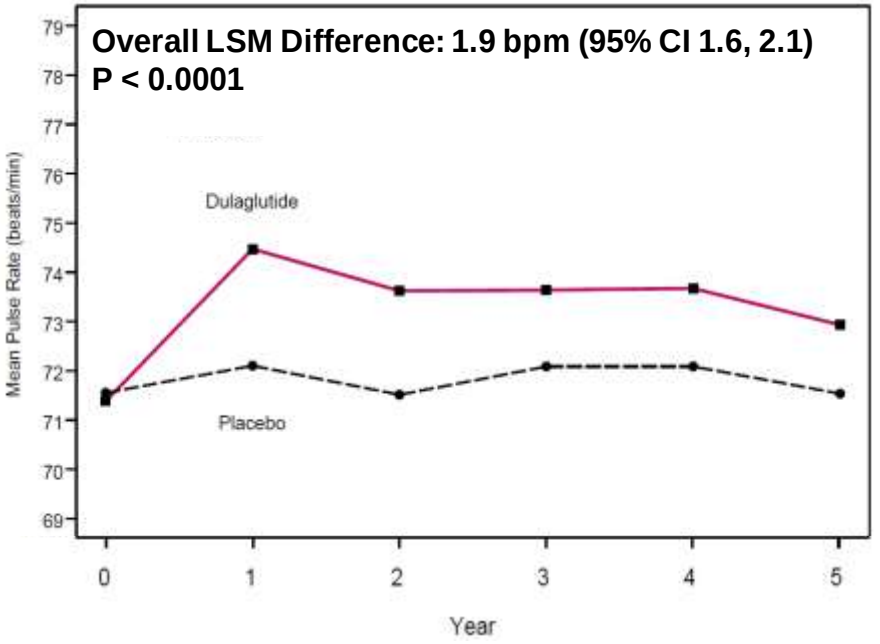
REWIND
Dulaglutide CV Outcomes Trial

# Dulaglutide's Effect on SBP & Heart Rate

## Systolic Blood Pressure



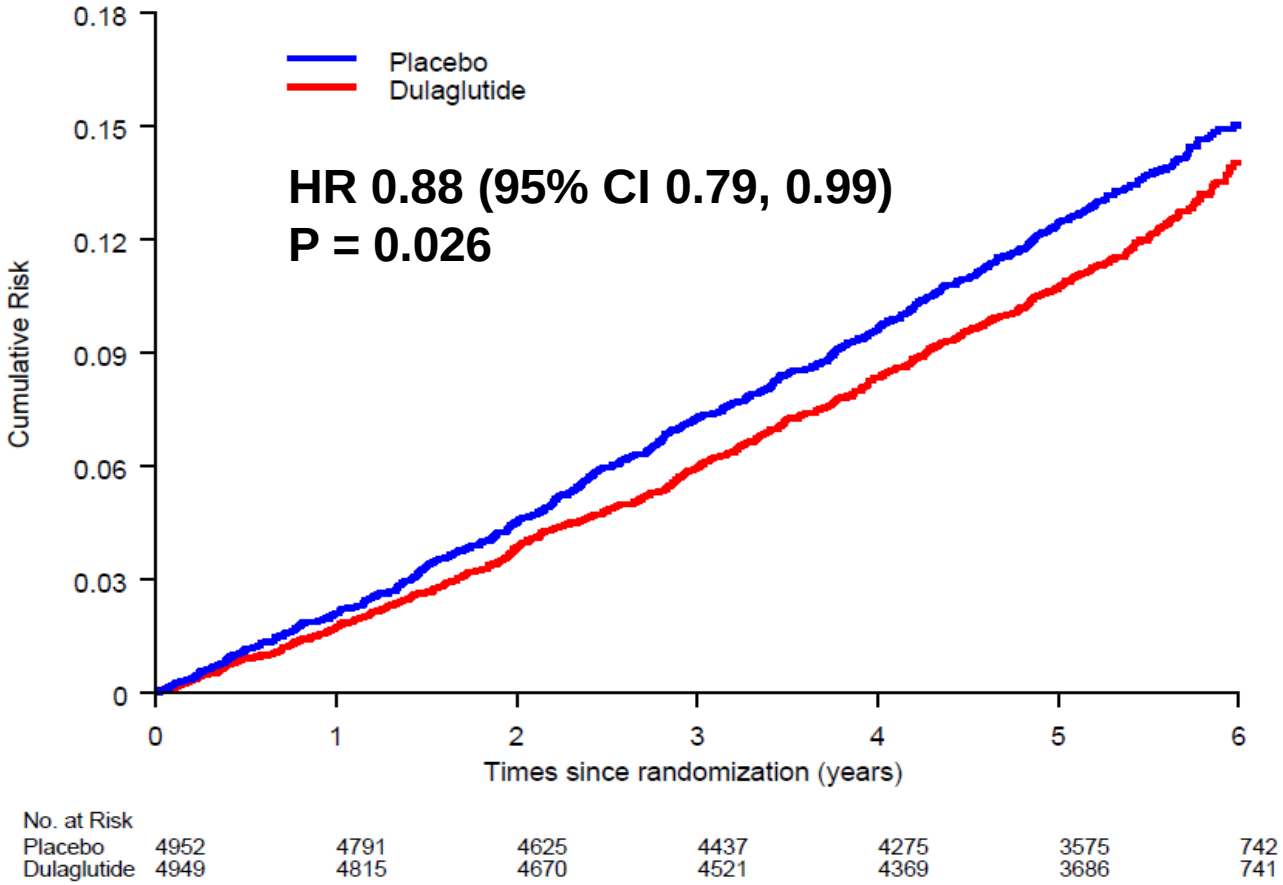

## Heart Rate



REWIND
Dulaglutide CV Outcomes Trial

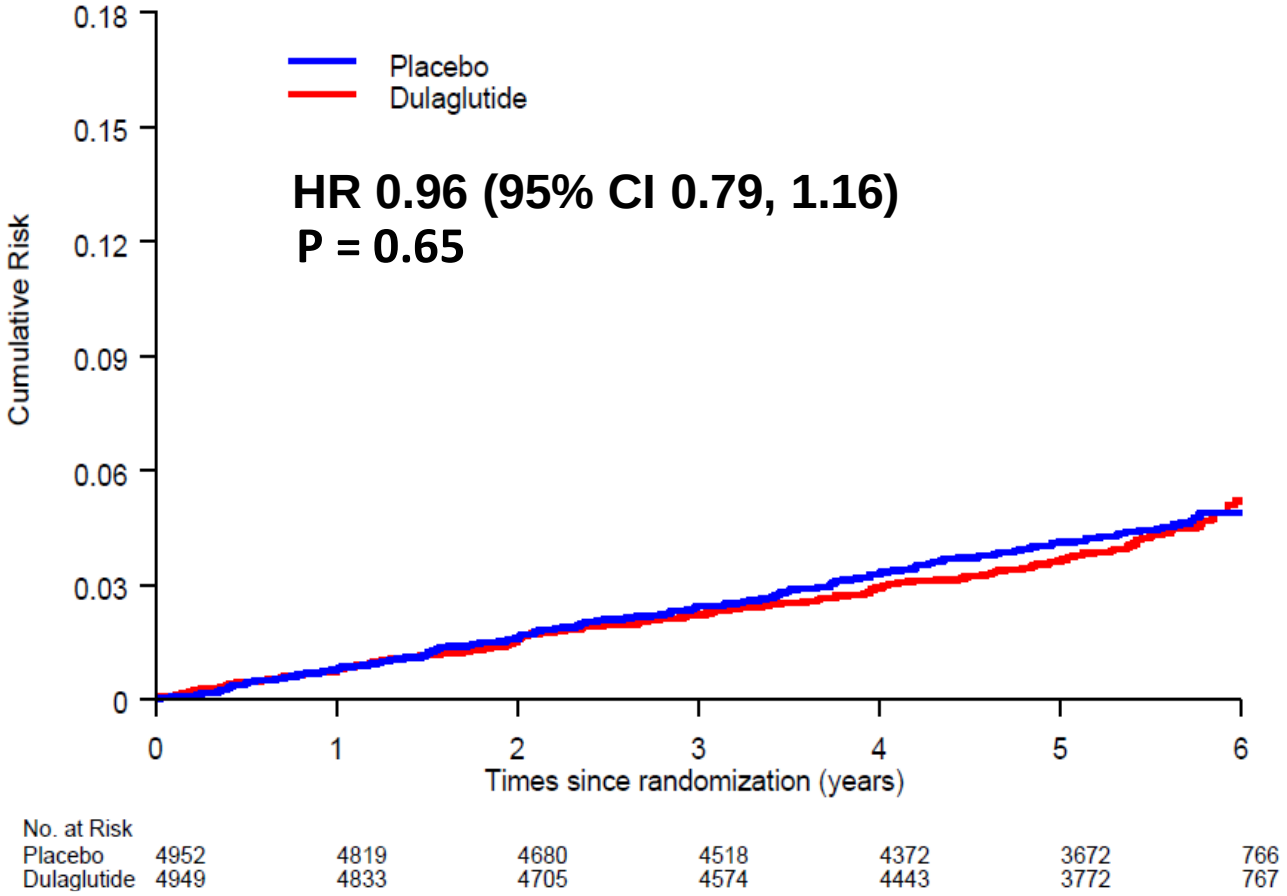
# Dulaglutide's Effect on the CV Composite

## Primary Outcome: 1st Occurrence of Nonfatal MI, Nonfatal Stroke, CV Death



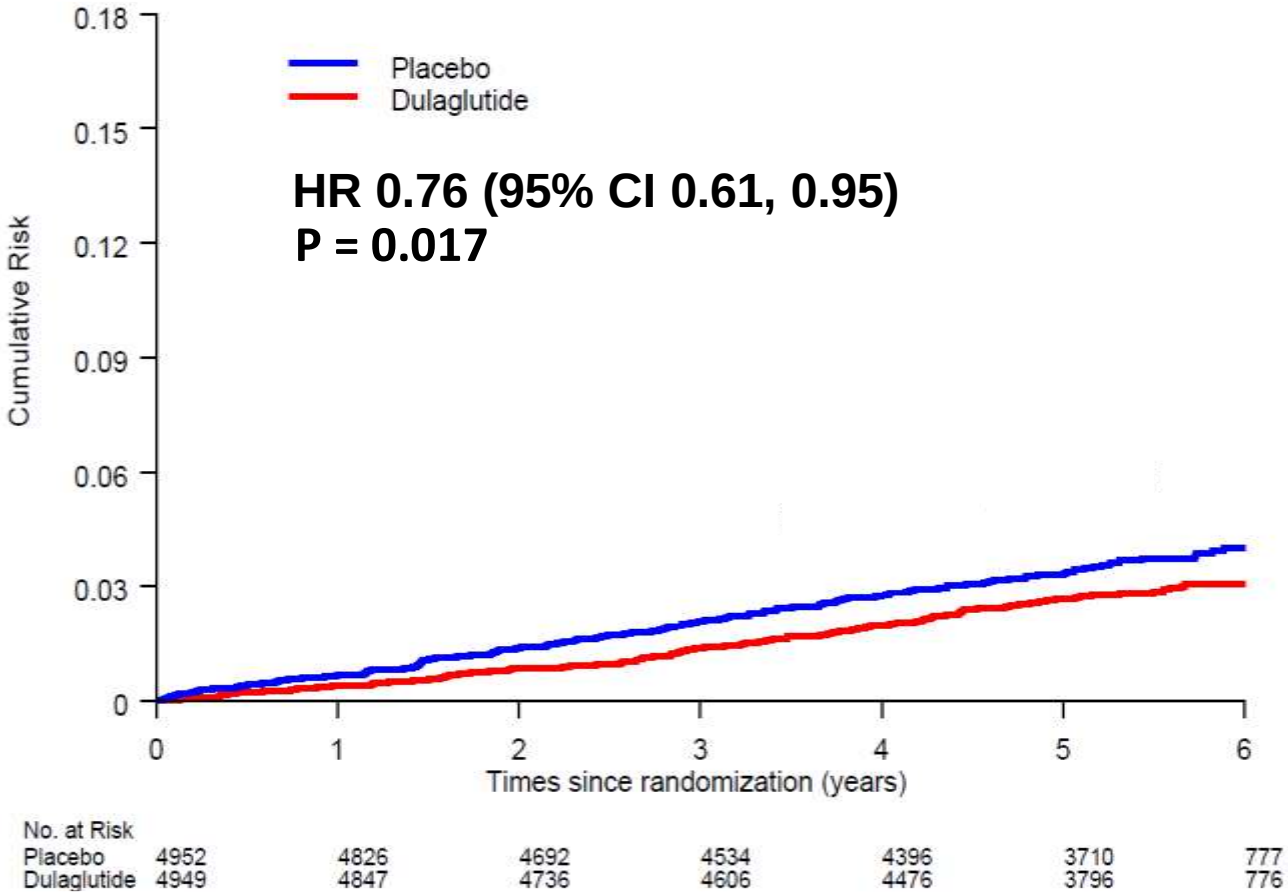
REWIND
Dulaglutide CV Outcomes Trial

# Dulaglutide's Effect on Nonfatal MI



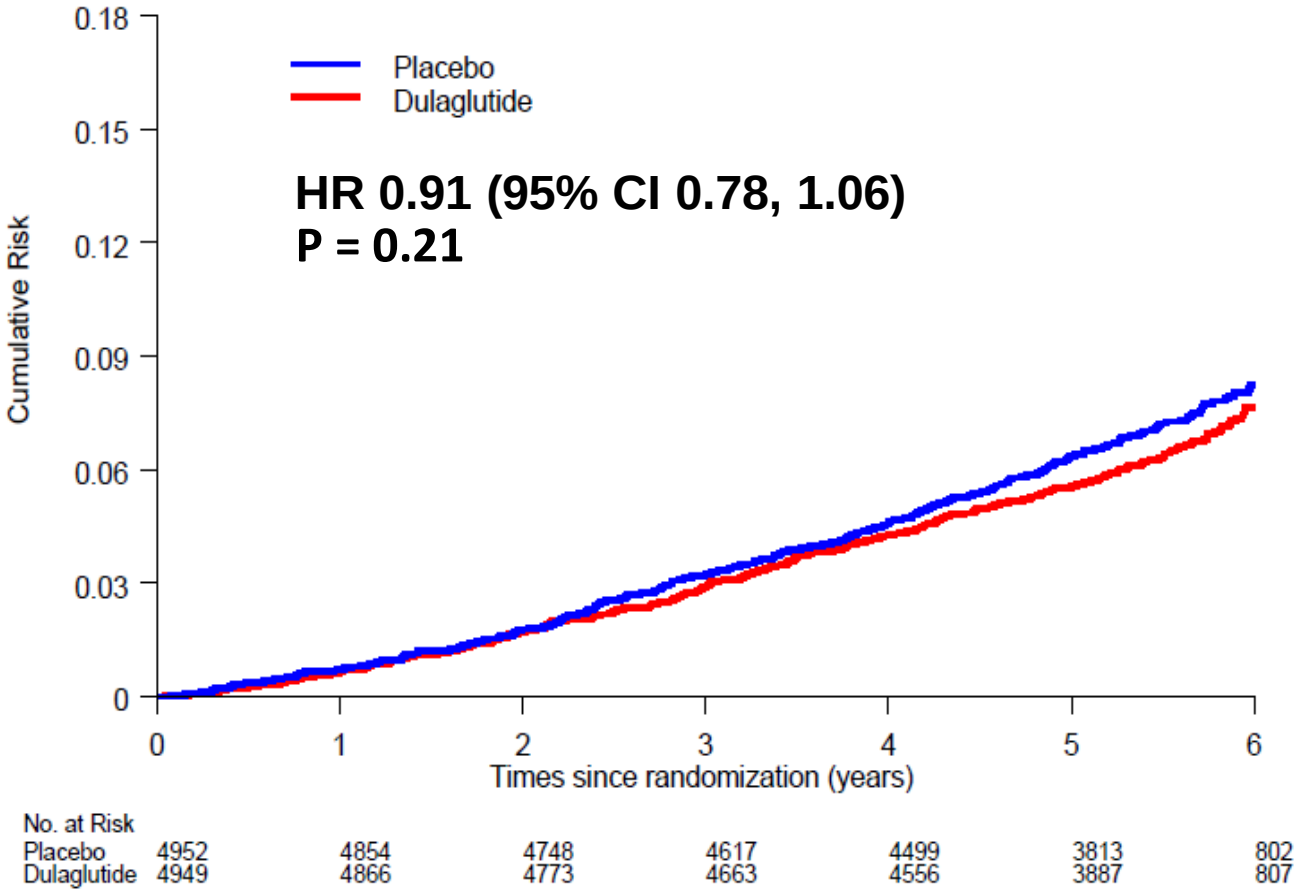
REWIND
Dulaglutide CV Outcomes Trial

# Dulaglutide's Effect on Nonfatal Stroke



REWIND
Dulaglutide CV Outcomes Trial

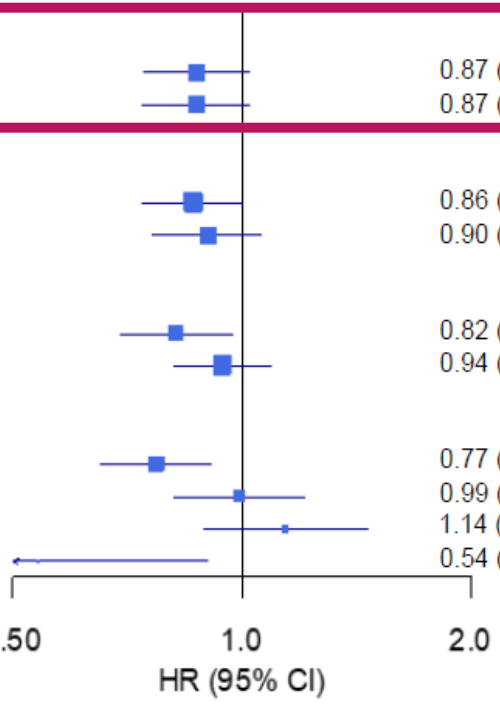
# Dulaglutide's Effect on CV Death



REWIND
Dulaglutide CV Outcomes Trial

# CV Composite in Prespecified Subgroups

| Subgroups | Dulaglutide Events/Total (%) | Dulaglutide Rate/100 py | Placebo Events/Total (%) | Placebo Rate/100 py | Hazard Ratio 95% CI | P value for Interaction |
|---|---|---|---|---|---|---|
| **History of CVD** | | | | | | |
| Prior CVD | 280 /1560 (17.9) | 3.7 | 315 /1554 (20.3) | 4.2 | 0.87 (0.74-1.02) | |
| No Prior CVD | 277 /3093 ( 8.9) | 1.7 | 317 /3128 (10.1) | 2.0 | 0.87 (0.74-1.02) | 0.970 |
| **Baseline HbA1c** | | | | | | |
| ≥ 7.2% | 328 /2610 (12.6) | 2.5 | 373 /2603 (14.3) | 2.9 | 0.86 (0.74-1.00) | |
| < 7.2% | 263 /2329 (11.3) | 2.2 | 289 /2334 (12.4) | 2.4 | 0.90 (0.76-1.06) | 0.746 |
| **BMI (kg/m^2)** | | | | | | |
| ≥ 32 | 254 /2281 (11.1) | 2.1 | 308 /2302 (13.4) | 2.6 | 0.82 (0.69-0.96) | |
| < 32 | 340 /2667 (12.7) | 2.5 | 355 /2650 (13.4) | 2.7 | 0.94 (0.81-1.09) | 0.214 |
| **Region** | | | | | | |
| Europe | 248 /2174 (11.4) | 2.2 | 315 /2165 (14.5) | 2.9 | 0.77 (0.65-0.90) | |
| Latin America | 191 /1511 (12.6) | 2.6 | 190 /1510 (12.6) | 2.6 | 0.99 (0.81-1.21) | |
| USA/Canada | 132 /1032 (12.8) | 2.4 | 117 /1039 (11.3) | 2.1 | 1.14 (0.89-1.47) | |
| Asia Pacific | 23 / 232 ( 9.9) | 1.9 | 41 / 238 (17.2) | 3.5 | 0.54 (0.32-0.89) | 0.008 |



REWIND
Dulaglutide CV Outcomes Trial

# Adverse Events of Special Interest

| | Dulaglutide N = 4949 | Placebo N= 4952 | P |
|---|---|---|---|
| **1st Study Drug Stopping** | 42.3% | 43.8% | 0.38 |
| **Acute Pancreatitis** | 0.5% | 0.3% | 0.11 |
| **Based on Imaging & Enzymes** | 0.1% | 0.1% | 0.71 |
| **Any Cancer** | 7.1% | 7.0% | 0.98 |
| **MTC or C-Cell Hyperplasia** | 1 | 0 | 0.32 |
| **Thyroid Cancer** | 0.1% | 0.1% | 0.21 |
| **Pancreatic Cancer** | 0.4% | 0.2% | 0.22 |

REWIND
Dulaglutide CV Outcomes Trial

# REWIND Findings in Context

| | ELIXA | LEADER | SUSTAIN 6 | EXSCEL | HARMONY |
|---|---|---|---|---|---|
| **N** | 6068 | 9340 | 3297 | 14752 | 9463 |
| **Drug Tested** | Lixi/d | Lira/d | Sema/wk | Exena/wk | Albig/wk |
| **Prior CVD** | 100% | 81% | 83% | 73% | 100% |
| **Mean Age** | 60 y | 64 y | 54 y | 62 y | 64 y |
| **Women** | 30% | 36% | 39% | 38% | 31% |
| **Median F/U** | 2.1 y | 3.8 y | 2.1 y | 3.2 y | 1.6 y |
| **DM Duration** | 9.2 y | 12.8 y | 13.9 y | 13.1 y | 14.2 y |
| **Baseline A1c** | 7.7% | 8.7% | 8.7% | 8.1% | 8.8% |
| **Baseline eGFR** | 76 | ~75 | ~75 | 76 | 79 |
| **Insulin Use** | 39% | 45% | 58% | 46% | 59% |

REWIND
Dulaglutide CV Outcomes Trial

# REWIND Findings in Context

| | ELIXA | LEADER | SUSTAIN 6 | EXSCEL | HARMONY | REWIND |
|---|---|---|---|---|---|---|
| **N** | 6068 | 9340 | 3297 | 14752 | 9463 | 9901 |
| **Drug Tested** | Lixi/d | Lira/d | Sema/wk | Exena/wk | Albig/wk | Dula/wk |
| **Prior CVD** | 100% | 81% | 83% | 73% | 100% | 31% |
| **Mean Age** | 60 y | 64 y | 54 y | 62 y | 64 y | 66 y |
| **Women** | 30% | 36% | 39% | 38% | 31% | 46% |
| **Median F/U** | 2.1 y | 3.8 y | 2.1 y | 3.2 y | 1.6 y | 5.4 y |
| **DM Duration** | 9.2 y | 12.8 y | 13.9 y | 13.1 y | 14.2 y | 10.5 y |
| **Baseline A1c** | 7.7% | 8.7% | 8.7% | 8.1% | 8.8% | 7.3% |
| **Baseline eGFR** | 76 | ~75 | ~75 | 76 | 79 | 77 |
| **Insulin Use** | 39% | 45% | 58% | 46% | 59% | 24% |

REWIND
Dulaglutide CV Outcomes Trial

# Conclusion

*The addition of dulaglutide could be considered for both primary & secondary CV prevention in middle-aged patients with type 2 diabetes & cardiovascular risk factors*

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

# SGLT2 inhibition

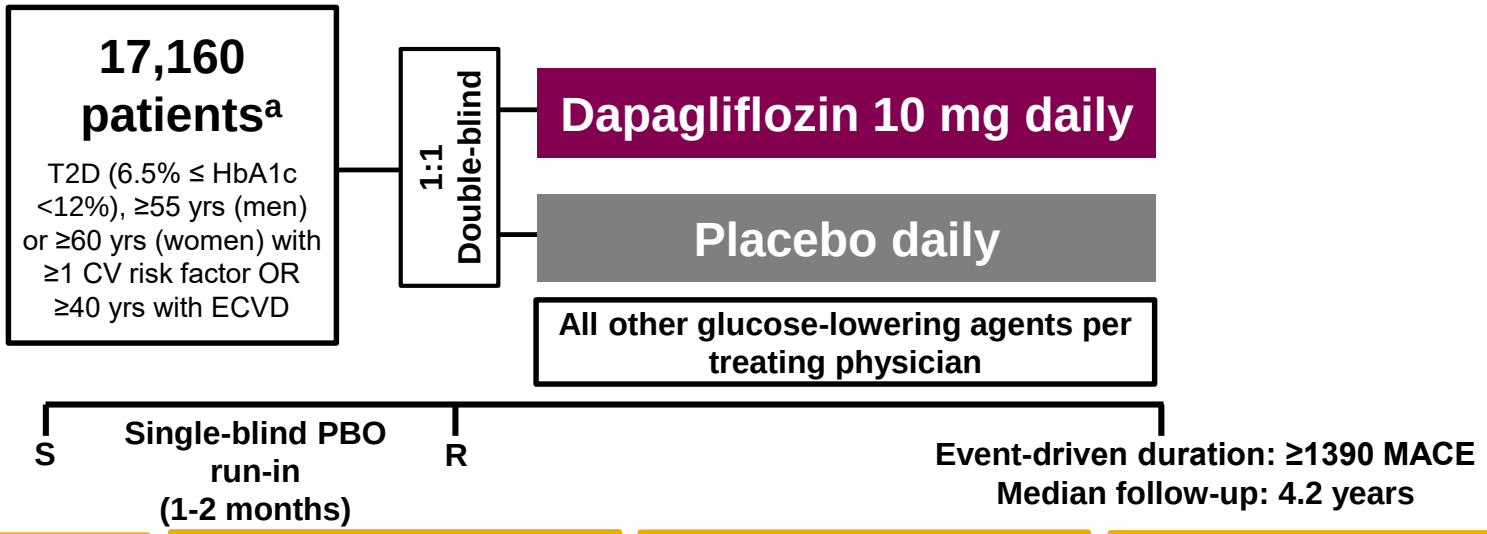
# DECLARE-TIMI 58 Trial

**ClinicalTrials.gov ID: NCT01730534**

DECLARE-TIMI 58, Dapagliflozin Effect on CardiovascuLAR Events – Thrombolysis In Myocardial Infarction 58

# A Multinational, Randomized, Double-blind, Placebo-controlled, Phase IIIb Cardiovascular Outcomes Trial

## Study Design[1,2,3]




### Primary safety endpoint

- Composite of CV death, nonfatal MI, or nonfatal ischemic stroke (MACE)

### Primary endpoints

- MACE
- Composite of hospitalisation for heart failure or CV death

### Secondary endpoints

- Renal composite endpoint (sustained ≥40% decrease in eGFR to eGFR <60 mL/min/bsa and/or ESRD and/or renal or CV death)
- All-cause mortality

### Additional safety endpoints

- Malignancies[b] (eg, bladder cancer)
- Liver events[b]
- DKA events[b]
- Amputations
- Fractures

### Data monitoring committee

- Periodically review safety
- Two preplanned efficacy reviews
- Assess bladder cancer every 8 events

[a]A total of 17,190 patients were randomized; however, 30 patients were excluded from all analyses because of significant good clinical practice violations at a single site for a different trial; [b]Blinded adjudication of events.

CV, cardiovascular; DKA, diabetic ketoacidosis; ECVD, established atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; ESRD = end-stage renal disease; HbA1c, glycated hemoglobin; MACE, major adverse cardiovascular events; MI, myocardial infarction; PBO, placebo; R, randomization; S, screening; T2D, type 2 diabetes; yrs, years.

1. Raz I et al. *Diabetes Obes Metab*. 2018;20:1102-1110; 2. Wiviott SD et al. *Am Heart J*. 2018;200:83-89; 3. Wiviott SD et al. Online ahead of print. *N Engl J Med.* 2018.

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# Key Inclusion/Exclusion Criteria

**Inclusion criteria:**

1. Female or male; age ≥40 years
2. Diagnosis of T2D
3. Increased CV risk according to 2 categories:
4. multiple risk factors for CV disease or established atherosclerotic CV disease

**Exclusion criteria:**

1. HbA1c ≥12% or <6.5%, with the proportion of patients with HbA1c of 6.5% to <7% capped at ~5%
2. Creatinine clearance <60 mL/min based on the Cockcroft-Gault equation
3. Unexplained hematuria
4. Lifetime history of bladder cancer or history of malignancy (other than nonmelanoma skin cancer) within the past 5 years
5. Recurrent urinary tract infections
6. Acute CV or cerebrovascular event within 8 weeks of randomization
7. Use of an SGLT2 inhibitor, pioglitazone, or rosiglitazone

.
CV, cardiovascular; HbA1c, glycated hemoglobin; SGLT2 , sodium-glucose cotransporter 2; T2D, type 2 diabetes.
Raz I et al. *Diabetes Obes Metab*. 2018;20:1102-1110.

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Raz I et al. *Diabetes Obes Metab*. 2018;20:1102-1110.

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# CV Risk Categories

## Multiple Risk Factors for CV Disease (MRF)

Age ≥55 years (men), ≥60 years (women)

**NOT HIGH RISK**

**AND** ≥1 additional risk factors:

- Dyslipidemia (≥1 of following)
  - LDL-C >130 mg/dL (>3.36 mmol/L)
  - On lipid-lowering therapy
- Hypertension (≥1 of following)
  - BP >140/90 mm Hg at enrollment
  - On antihypertensive therapy
- Current smoking
  - ≥5 cigarettes/day for ≥1 year

## Established Atherosclerotic CV Disease (ECVD)

Age ≥40 years

**AND** ≥1 additional diagnoses:

- Ischemic heart disease (any of following)
  - MI
  - PCI
  - CABG
  - ≥50% coronary stenosis in ≥2 coronary arteries
- Cerebrovascular disease (any of following)
  - Ischemic stroke
  - Carotid stenting or endarterectomy
- Peripheral artery disease (any of following)
  - Peripheral arterial stenting or surgical revascularization
  - Lower extremity amputation as a result of PAD
  - Symptomatic IC and ABI <0.90 in last 12 mo.

ABI, ankle-brachial index; BP, blood pressure; CABG, coronary artery bypass grafting; CV, cardiovascular; IC, intermittent claudication; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; mo., month;
PAD, peripheral artery disease; PCI, percutaneous coronary intervention.

Wiviott SD et al. Supplemental materials. *Am Heart J*. 2018;200:83-89.

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# DECLARE: Definition of hospitalisation for Heart Failure

- A heart failure event includes hospitalisation for heart failure (hHF) and may include urgent outpatient visits. HF hospitalisations should remain delineated from urgent visits.

- hHF is defined as an event that meets all of the following criteria:
  - Admitted to the hospital with a primary diagnosis of HF
  - Length-of-stay in hospital extends for at least 24 hours
  - Exhibits documented new or worsening symptoms due to HF on presentation, including at least one of the following:
    - Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea); decreased exercise tolerance; fatigue; other symptoms of worsened end-organ perfusion or volume overload
  - Objective evidence of new or worsening HF, consisting of ≥ 2 physical examination findings or 1 physical examination finding and ≥ 1 laboratory criterion:
    - Physical examination finding considered to be due to HF, including new or worsened:
      - Peripheral edema
      - Increasing abdominal distension or ascites (in absence of primary hepatic disease)
      - Pulmonary rales/crackles/crepitations
      - Increased jugular venous pressure and/or hepatojugular reflux
      - S3 gallop
      - Clinically significant or rapid weight gain thought to be related to fluid retention

BNP = B-type natriuretic peptide

Wiviott SD et al. Supplementary material. *Am Heart J*. 2018;200:83-89.

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# Medical History

| | DAPA 10 mg (N=8582) | Placebo[a] (N=8578) |
|---|---|---|
| **Baseline CV risk category** | | |
| Patients with multiple CV risk factors | 5108 (59.5) | 5078 (59.2) |
| Patients with established CV disease | 3474 (40.5) | 3500 (40.8) |
| **Established CV disease** | | |
| History of coronary artery disease | 2824 (32.9) | 2834 (33.0) |
| History of peripheral artery disease | 522 (6.1) | 503 (5.9) |
| History of cerebrovascular disease | 653 (7.6) | 648 (7.6) |
| **History of heart failure** | 852 (9.9) | 872 (10.2) |

[a]P=NS for all between group comparisons. Results are listed as n (%) unless noted.
CV, cardiovascular; DAPA, dapagliflozin.
Wiviott SD et al. Online ahead of print. *New Engl J Med*. 2018.

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# Baseline Medication Use

| | DAPA 10 mg (N=8582) | Placebo[a] (N=8578) |
|---|---|---|
| **Glucose-lowering therapies** | | |
| Metformin | 7020 (81.8) | 7048 (82.2) |
| Insulin | 3567 (41.6) | 3446 (40.2) |
| Sulfonylurea | 3615 (42.1) | 3707 (43.2) |
| DPP-4 inhibitor | 1418 (16.5) | 1470 (17.1) |
| GLP-1 RA | 397 (4.6) | 353 (4.1) |
| **Cardiovascular therapies** | | |
| Antiplatelet agents | 5245 (61.1) | 5242 (61.1) |
| ACEI or ARB | 6977 (81.3) | 6973 (81.3) |
| Beta-blocker | 4498 (52.4) | 4532 (52.8) |
| Statin or ezetimibe | 6432 (74.9) | 6436 (75.0) |
| Diuretics | 3488 (40.6) | 3479 (40.6) |

[a]P=NS for all between group comparisons. Results are listed as n (%) unless noted.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; DAPA, dapagliflozin; DPP-4, dipeptidyl peptidase-4; GLP-1 RA = glucagon-like peptide-1 receptor agonist.

Wiviott SD et al. Online ahead of print. *New Engl J Med.* 2018.

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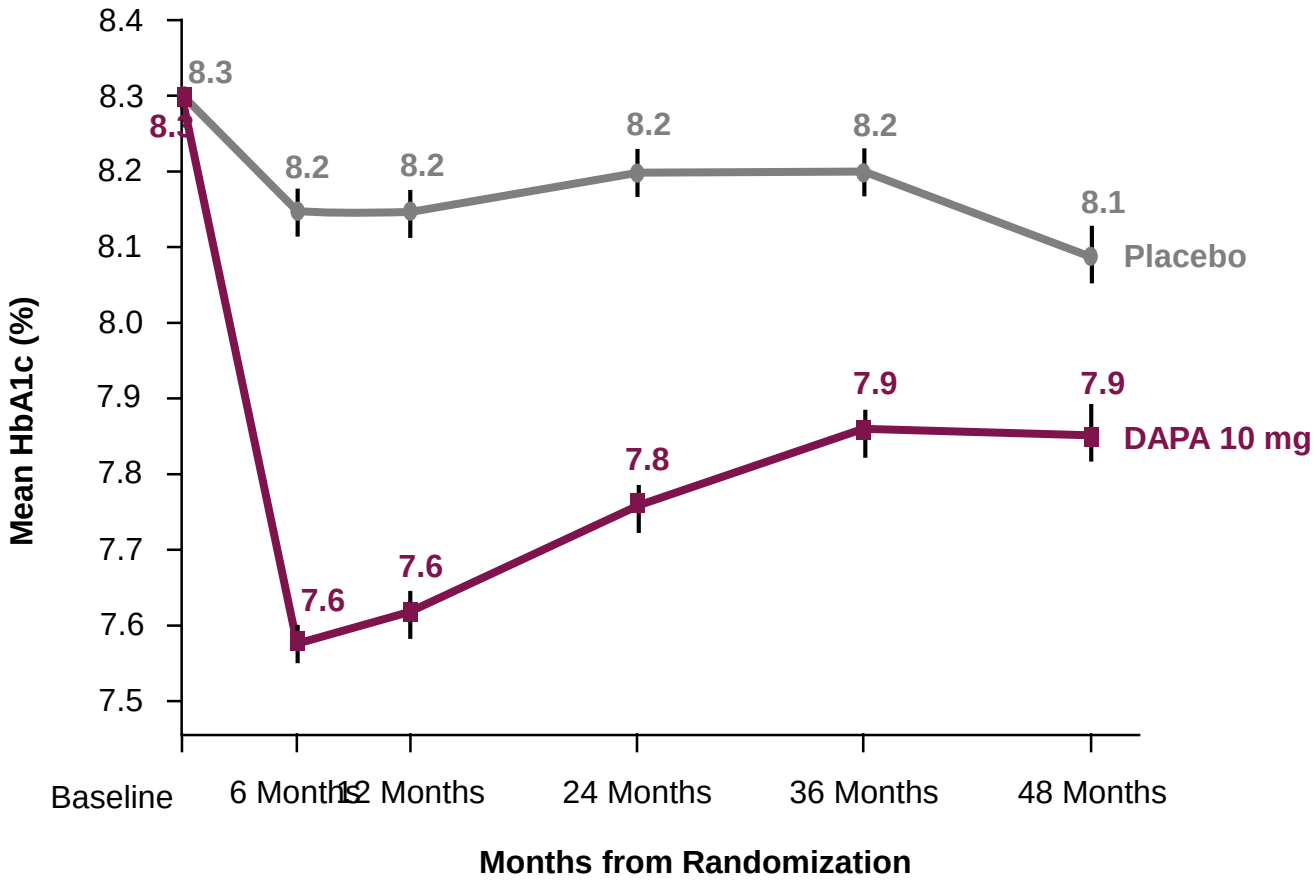
# Adjusted Mean HbA1c Over Time




DAPA, dapagliflozin; HbA1c, glycated hemoglobin.

Wiviott SD et al. Article and supplementary appendix online ahead of print. *New Engl J Med*. 2018.

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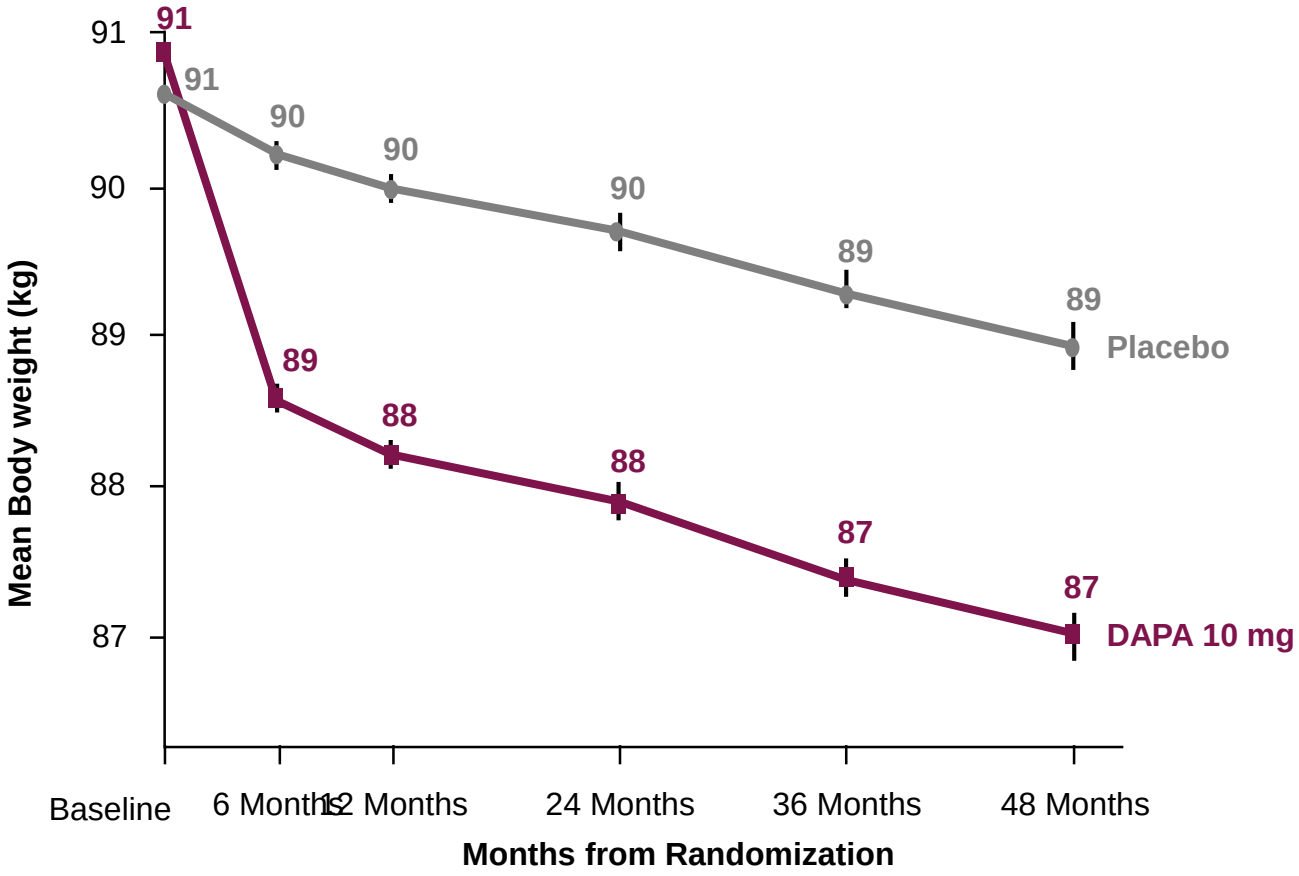
# Adjusted Mean Body Weight Over Time




DAPA, dapagliflozin.

Wiviott SD et al. Article and supplementary appendix online ahead of print. *New Engl J Med*. 2018.

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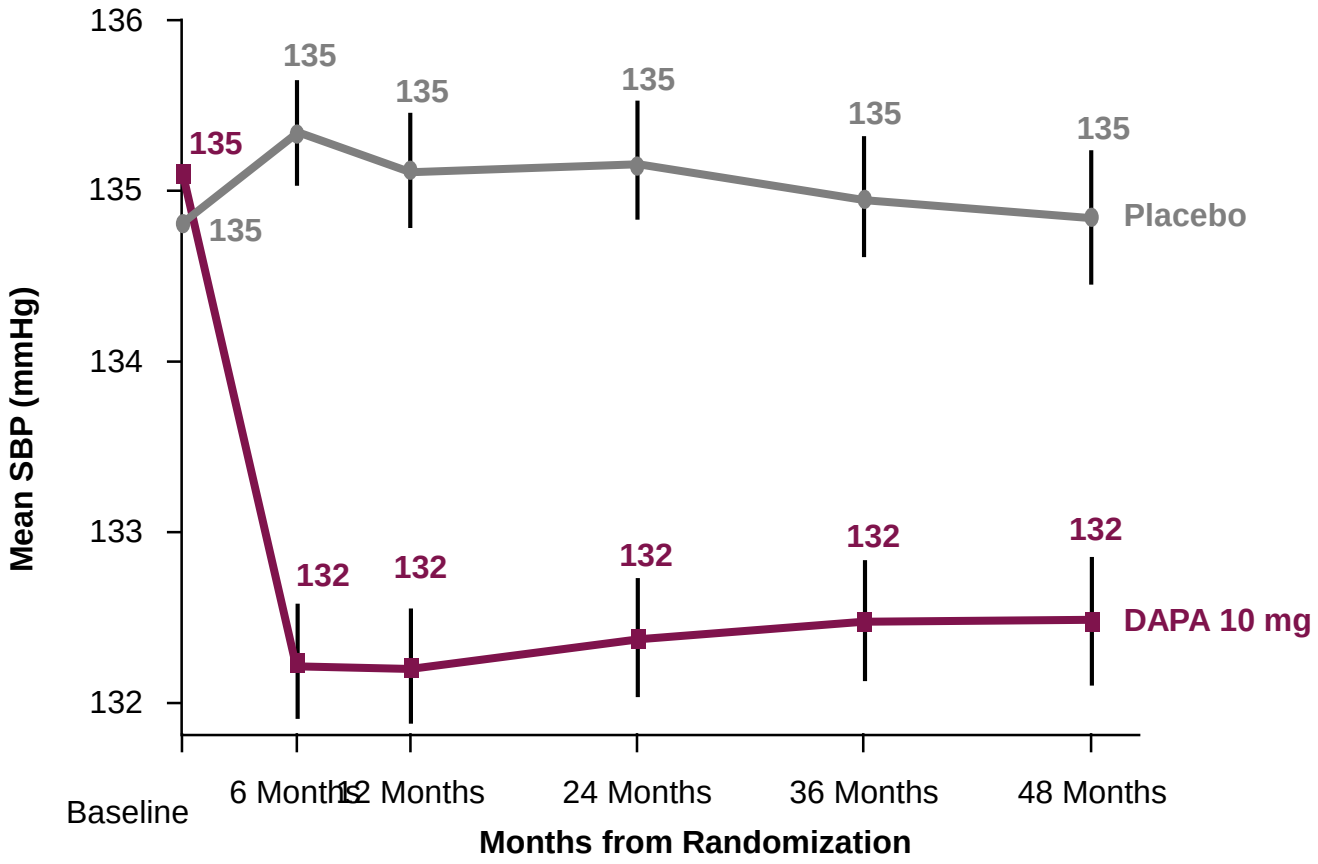
# Adjusted Mean Systolic Blood Pressure Over Time




DAPA, dapagliflozin; SBP, systolic blood pressure.

Wiviott SD et al. Article and supplementary appendix online ahead of print. *New Engl J Med.* 2018.

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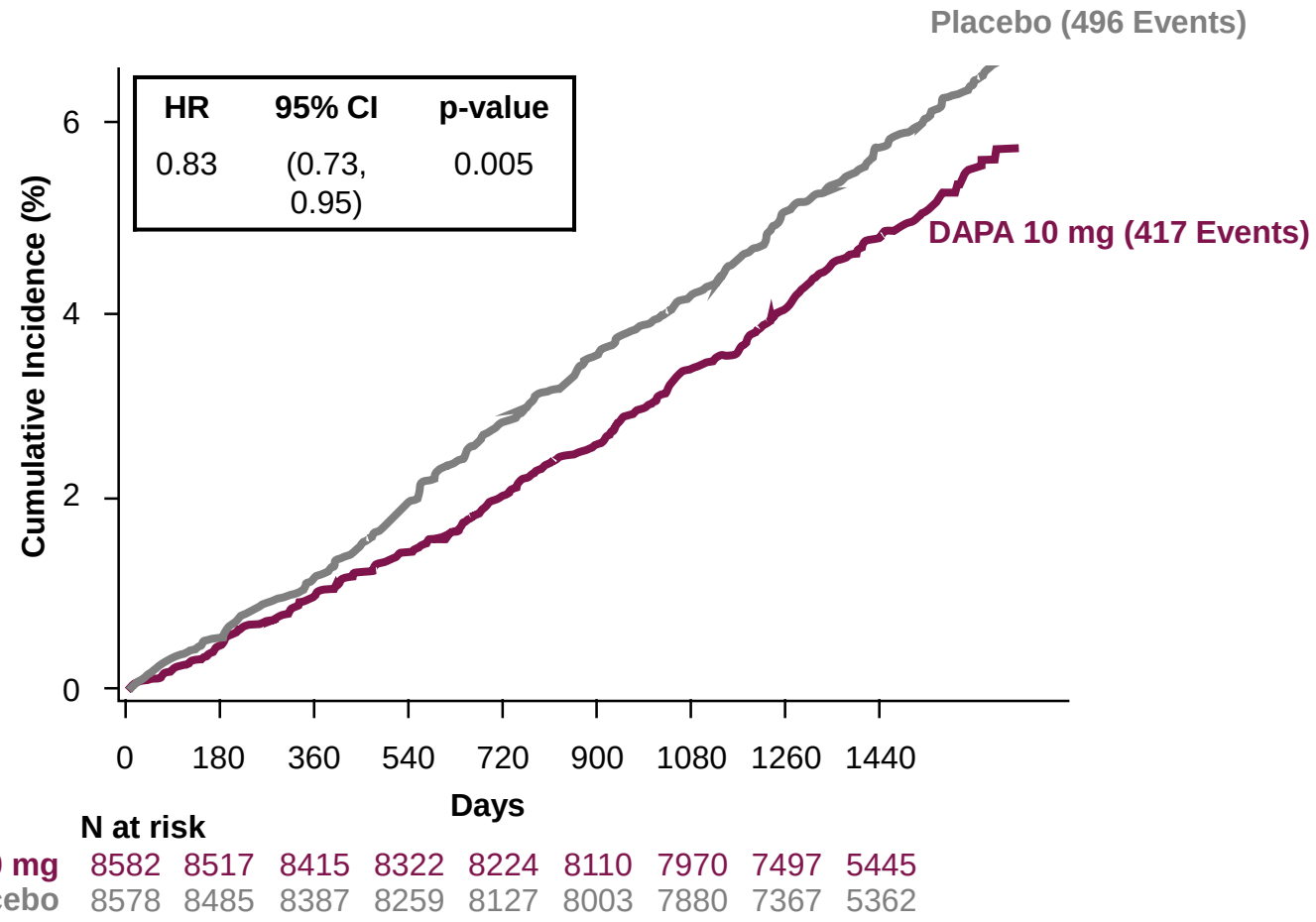
# DECLARE-TIMI 58
# Primary Efficacy Endpoints

DECLARE-TIMI 58, Dapagliflozin Effect on CardiovascuLAR Events – Thrombolysis In Myocardial Infarction 58

# Primary Endpoint: Composite of hHF or CV Death




N at risk is the number of patients at risk at the beginning of the period.

CV, cardiovascular; DAPA, dapagliflozin; hHF, hospitalisation for heart failure.

Wiviott SD et al. Online ahead of print. *New Engl J Med.* 2018.

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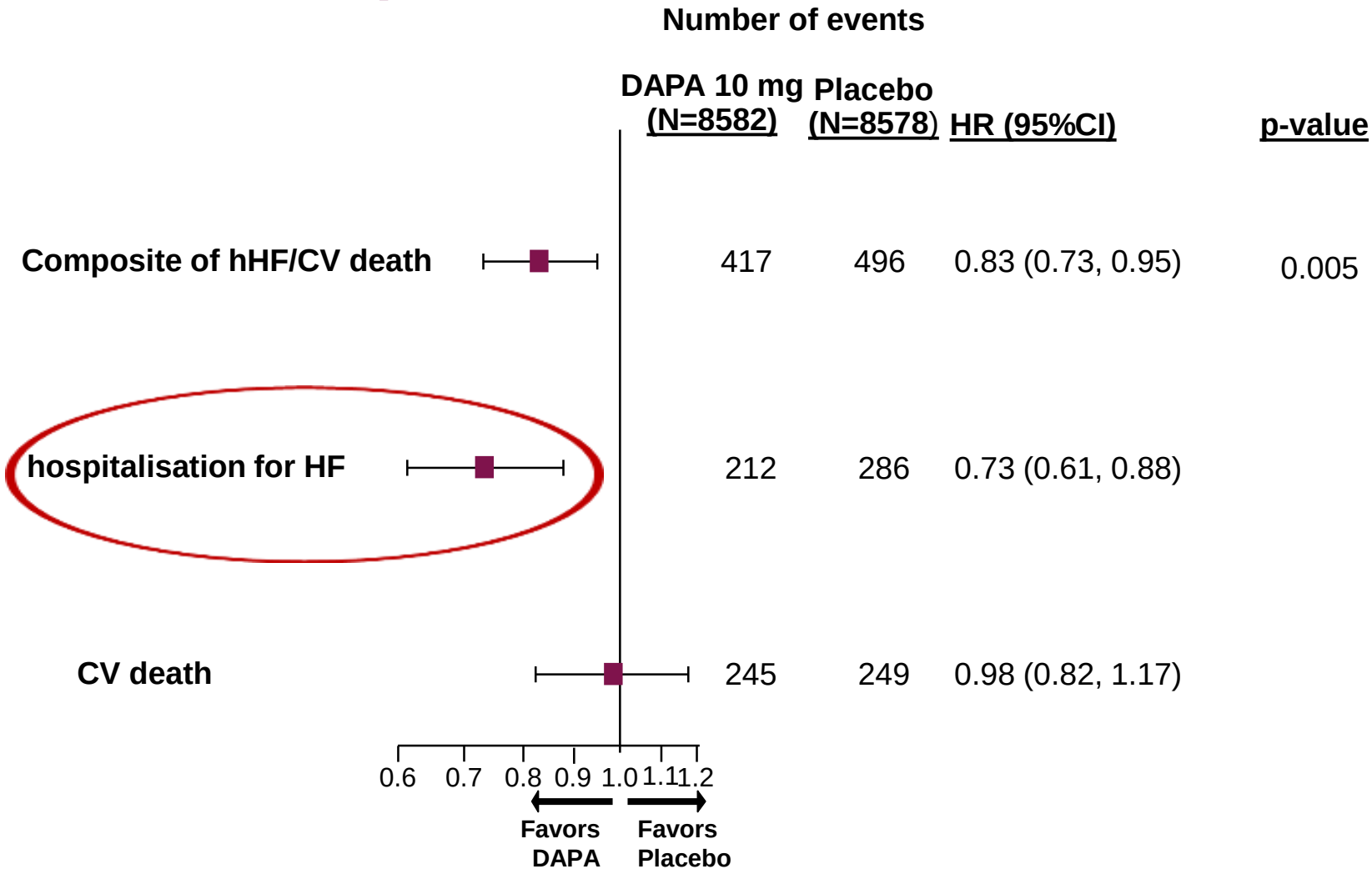
# Primary Endpoint: Composite of hHF or CV death and the Individual Components




Two-sided p-value is shown for the primary efficacy composite outcome of CV death or hHF.
CV, cardiovascular; DAPA, dapagliflozin; HF, heart failure; hHF, hospitalisation for heart failure.
Wiviott SD et al. Online ahead of print. *New Engl J Med.* 2018.

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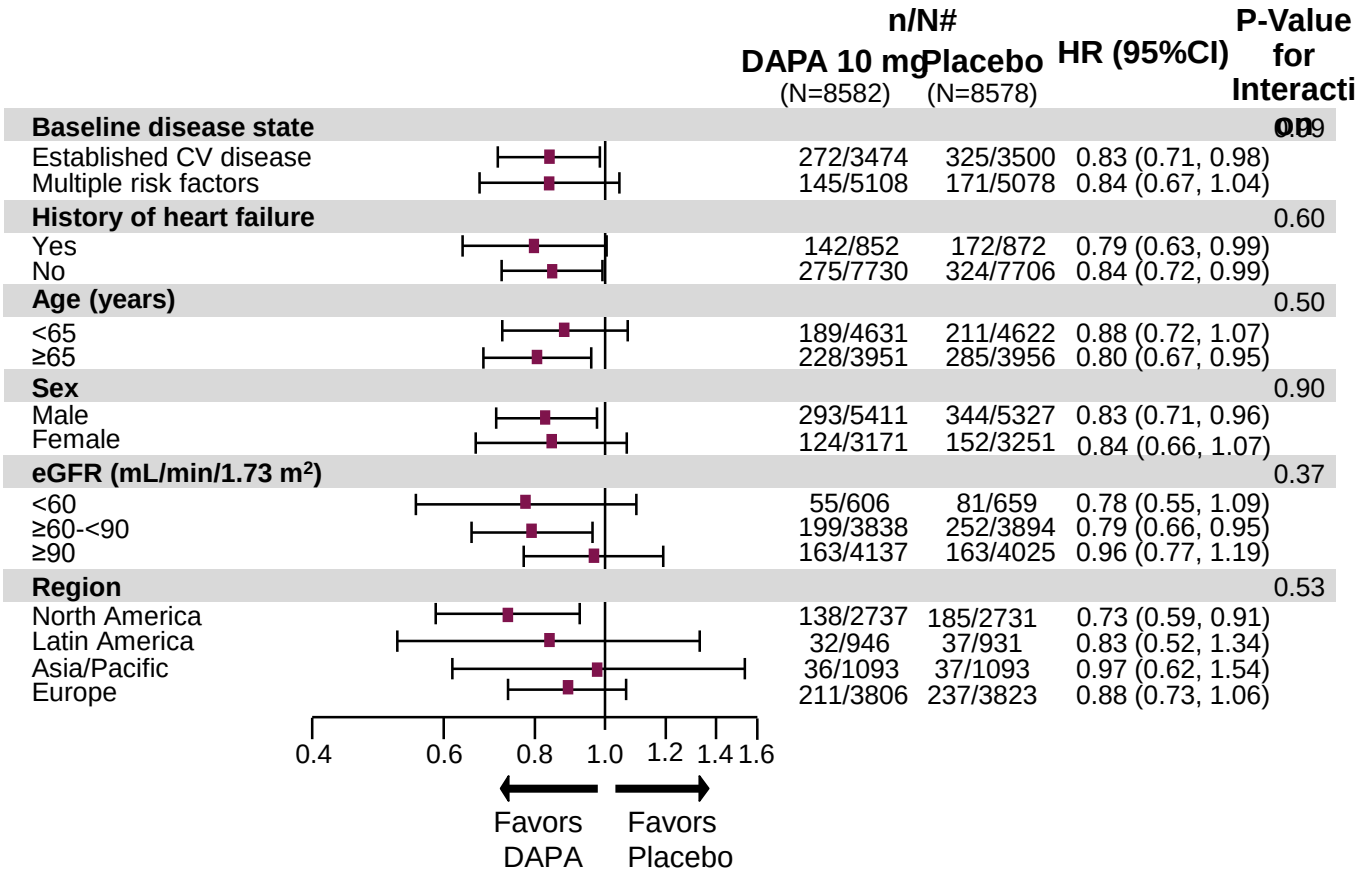
# Primary Endpoint: hHF or CV Death by Subgroups[1,2]




N, number of patients; N#, number of patients within subgroup category; n, number of events.

CV, cardiovascular, DAPA, dapagliflozin; eGFR, estimated glomerular filtration rate; hHF, hospitalisation for heart failure. .

1. Wiviott SD et al. Article and supplementary appendix online ahead of print. *New Engl J Med*. 2018. 2. In House Data, AstraZeneca Pharmaceuticals LP. D1693C00001. September 21, 2018.

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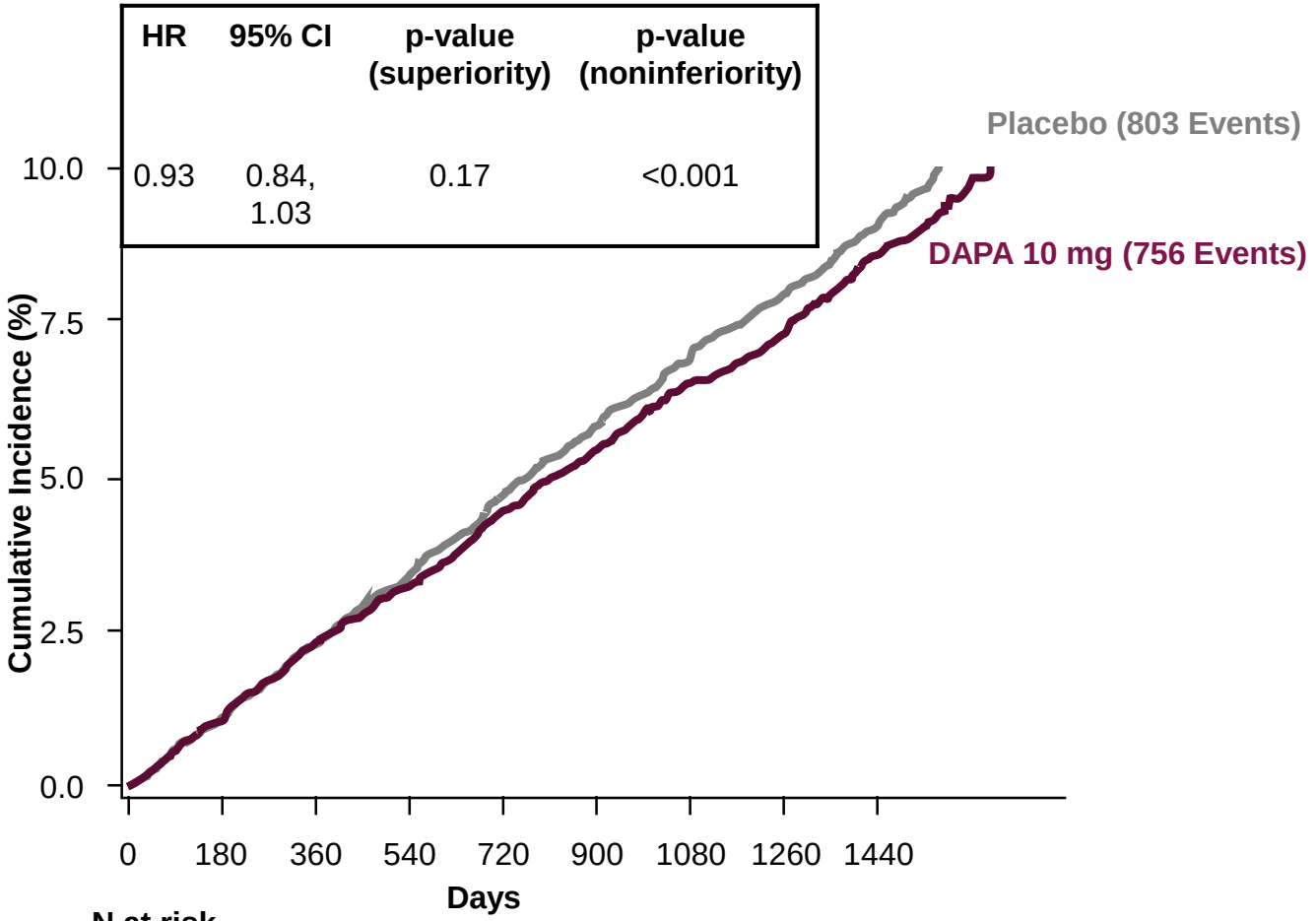
# Primary Endpoint: MACE




**N at risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **DAPA 10 mg** | 8582 | 8466 | 8303 | 8166 | 8017 | 7873 | 7708 | 7237 | 5225 |
| **Placebo** | 8578 | 8433 | 8281 | 8129 | 7969 | 7805 | 7649 | 7137 | 5158 |

N at risk is the number of patients at risk at the beginning of the period.
DAPA, dapgliflozin; MACE, major adverse cardiovascular events.
Wiviott SD et al. Online ahead of print. *New Engl J Med*. 2018.

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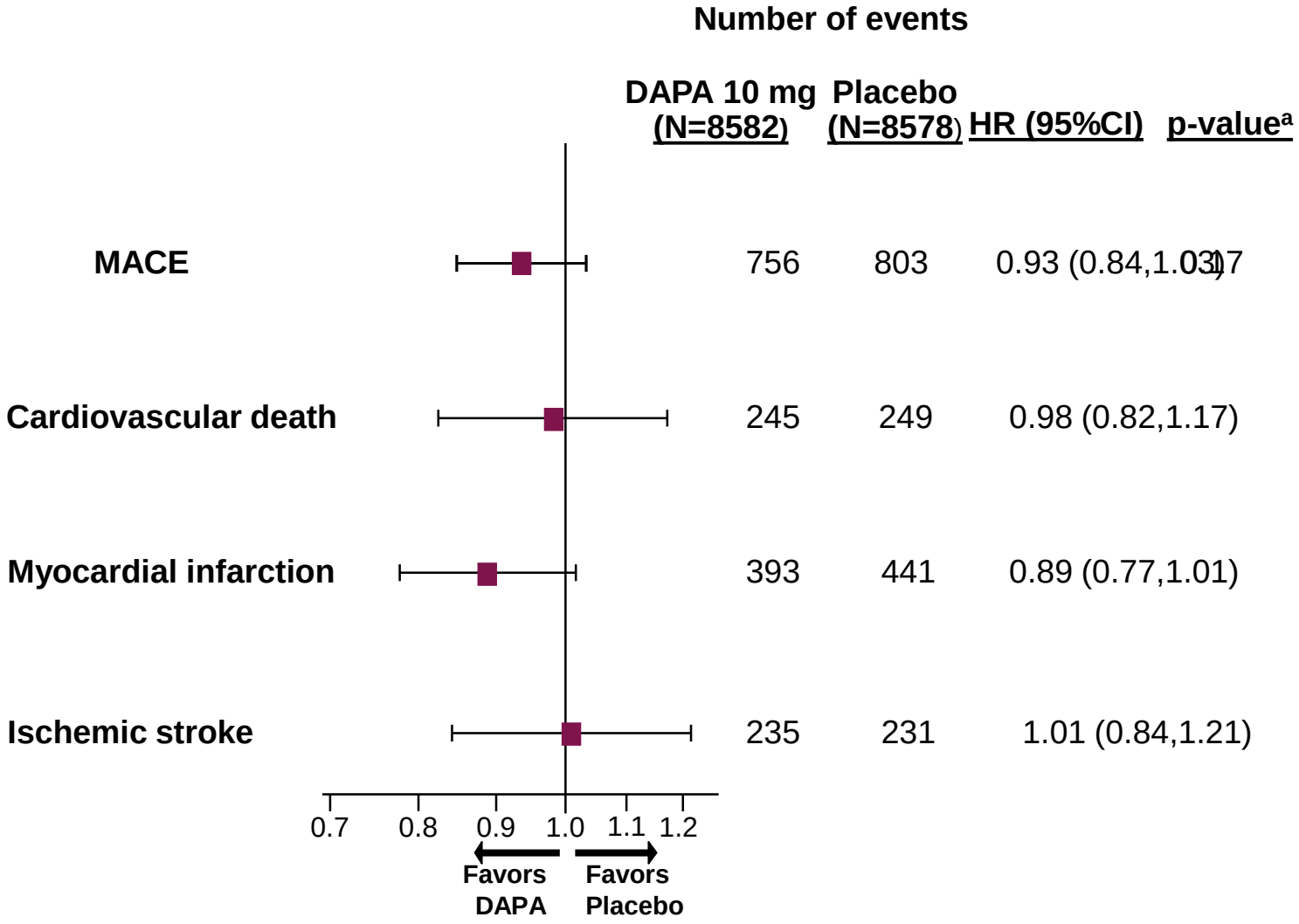
# Primary Endpoint: Composite of MACE and the Individual Components




[a]Two-sided p-value is shown for the primary efficacy outcome of MACE; p-value for noninferiority was p<0.001.

DAPA, dapagliflozin; MACE, major adverse cardiovascular events.

Wiviott SD et al. Online ahead of print. *New Engl J Med*. 2018.

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# AEs of Special Interest and Other Safety Events

| Adverse Event, n (%) | DAPA 10 mg (N=8574) | Placebo (N=8569) |
|---|---|---|
| Malignancy[a] | 481 (5.6) | 486 (5.7) |
| Bladder cancer[a] | 26 (0.3) | 45 (0.5) |
| Hepatic event[a] | 82 (1.0) | 87 (1.0) |
| Major hypoglycemia | 58 (0.7) | 83 (1.0) |
| Fracture | 457 (5.3) | 440 (5.1) |
| Acute kidney injury | 125 (1.5) | 175 (2.0) |
| Symptoms of volume depletion | 213 (2.5) | 207 (2.4) |
| Hypersensitivity reaction[b] | 32 (0.4) | 36 (0.4) |
| Urinary tract infection[b] | 127 (1.5) | 133 (1.6) |
| Genital infection[b,c] | 76 (0.9) | 9 (0.1) |
| Diabetic ketoacidosis[d] | 27 (0.3) | 12 (0.1) |
| Amputation | 123 (1.4) | 113 (1.3) |
| Fournier's gangrene | 1 (0.01) | 5 (0.06) |

[a]Adjudicated; [b]Leading to discontinuation of the trial regimen or considered to be serious AEs; [c]Serious AEs were rare, with only 2 events in each group; [d]Adjudicated as definite or probable.

AE, adverse event; DAPA, dapagliflozin.

Wiviott SD et al. Article and supplementary appendix online ahead of print. *New Engl J Med*. 2018

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AE, adverse event; DAPA, dapagliflozin.

Wiviott SD et al. Article and supplementary appendix online ahead of print. *New Engl J Med*. 2018

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# Summary

- **The primary composite outcome of hHF or CV death was significantly reduced with dapagliflozin compared with placebo.**
  - RRR was ~17% in patients with or without established CV disease at baseline
  - Effect was on top of standard of care for CV risk factor management,
  - Consistent regardless of history of established CV disease or heart failure
  - Reduction in the composite was driven by a ~27% RRR in hHF
  - **Majority did not have a history of heart failure**
- Fewer MACE events were observed in patients receiving dapagliflozin than placebo; however, this did not reach statistical significance.
- Fewer patients in the dapagliflozin group than in the placebo group reported a serious adverse event (34.1% vs 36.2%).
  - **DKA[a] and genital infections[b] were more common with dapagliflozin**
  - **No imbalance in risk of amputation, fracture, or Fournier's gangrene was observed between groups**

[a]Adjudicated as definite or probable; [b]Leading to discontinuation of the trial regimen or considered to be serious AEs.
CV, cardiovascular; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; hHF, hospitalisation for heart failure; MACE, major adverse cardiovascular events; RRR, relative risk reduction.
Wiviott SD et al. Article and supplementary appendix online ahead of print. *New Engl J Med.* 2018.

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# Summary CV benefits

- **GLP-1** RA s/c injections
- Liraglutide 1.8mg
- Semaglutide weekly ?oral
- (Exenatide MR)
- Dulaglutide

- **DPP-IV** –No Cardiovascular benefit
- *Linagliptin vs Glimepiride (CAROLINA) –non-inferior risk of CV event*

- **SGLT2i** - 3 shown to reduce Heart failure
- CV mortality reduction –Empagliflozin/Canagliflozin
- MACE –MI –NS ?Dapagliflozin

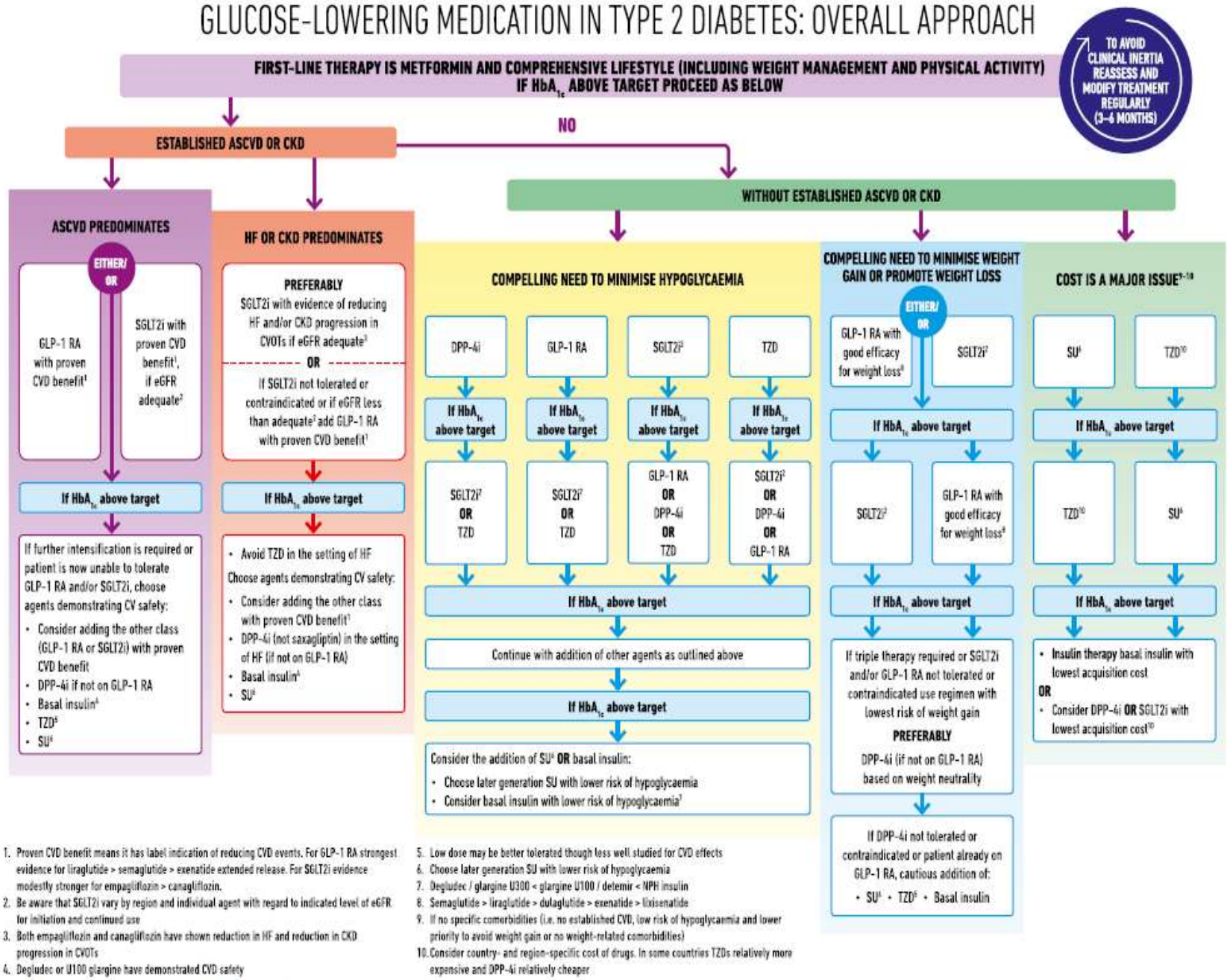
Diabetologia
https://doi.org/10.1007/s00125-018-4729-5

CONSENSUS REPORT

# Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Melanie J. Davies[1,2] · David A. D'Alessio[3] · Judith Fradkin[4] · Walter N. Kernan[5] · Chantal Mathieu[6] · Geltrude Mingrone[7,8] · Peter Rossing[9,10] · Apostolos Tsapas[11] · Deborah J. Wexler[12,13] · John B. Buse[14]

© European Association for the Study of Diabetes and American Diabetes Association 2018




1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycaemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

**Fig. 2** Glucose-lowering medication in type 2 diabetes: overall approach

## UNANSWERED QUESTIONS :

IS CV BENEFIT –due to risk factor reduction or class of effect ?

HOW DO SGLT2i reduce CV death/hHF ?

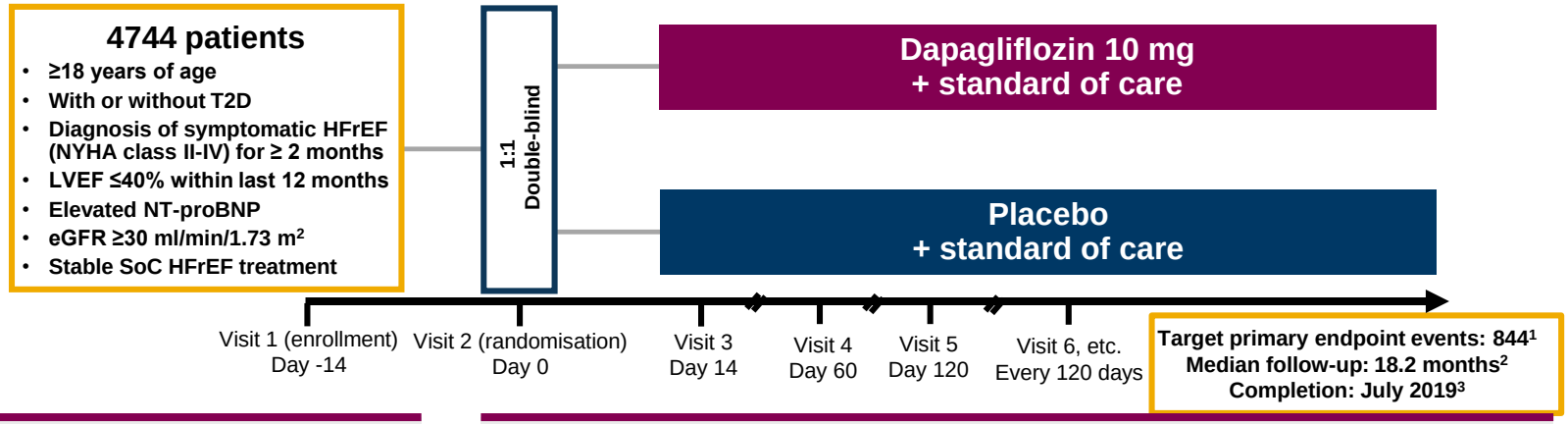
SGLT2 +GLP-1 –Do they lead to additive effects ?

What are the effects of other combinations ?
Eg PIOGLITAZONE +SLGT2i

Do patients at lower CV risk benefit or will an increase population exposure in type 2 DM lead to risks of …….DKA ?

CV benefits in type I DM ?

# DAPAHF: Assessing Dapagliflozin in Patients with Chronic HFrEF With or Without T2D[1-4]




## Primary Endpoint

- Time to first occurrence of any of the components of the composite: CV death or hHF or an urgent HF visit

## Secondary Endpoints

- Time to first occurrence of either of the components of the composite: CV death or hHF
- Total number of (first and recurrent) hHF and CV death
- Change from baseline measured at 8 months in the total symptom score of the KCCQ
- Time to first occurrence of any of the components of the composite: ≥50% sustained decline in eGFR or reaching ESRD or renal death
- Time to death from any cause

CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESRD = end stage renal disease; HbA1c = glycated haemoglobin; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; hHF = hospitalisation for heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association; SoC = standard of care; T2D = type 2 diabetes.

1. McMurray JJV et al. Article and supplementary appendix. *Eur J Heart Fail.* 2019;21:665-675; 2. McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France; 3. Study NCT03036124. ClinicalTrials.gov website. Accessed August 19, 2019. 4. McMurray JJV et al. *Eur J Heart Fail*. 2019;doi: 10.1002/ejhf.1548. Accessed July 16, 2019.



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# Key Baseline Characteristics

| Characteristic | Dapagliflozin (n=2373) | Placebo (n=2371) |
|---|---|---|
| Mean age (yr) | 66 | 67 |
| Male (%) | 76 | 77 |
| NYHA class II/III/IV (%) | 68/31/1 | 67/32/1 |
| Mean LVEF (%) | 31 | 31 |
| Median NT pro BNP (pg/mL) | 1428 | 1446 |
| Mean systolic BP (mmHg) | 122 | 122 |
| Ischaemic aetiology (%) | 55 | 57 |
| Mean eGFR (mL/min/1.73m$^2$) | 66 | 66 |
| Prior diagnosis T2D (%) | 42 | 42 |
| Any baseline T2D (%)[a] | 45 | 45 |

[a] Includes 82 dapagliflozin and 74 placebo patients with previously undiagnosed diabetes i.e. two HbA1c ≥6.5% (≥48 mmol/mol).

BP = blood pressure; eGFR = estimated glomerular filtration rate; NT pro BNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; T2D = type 2 diabetes.



McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France.

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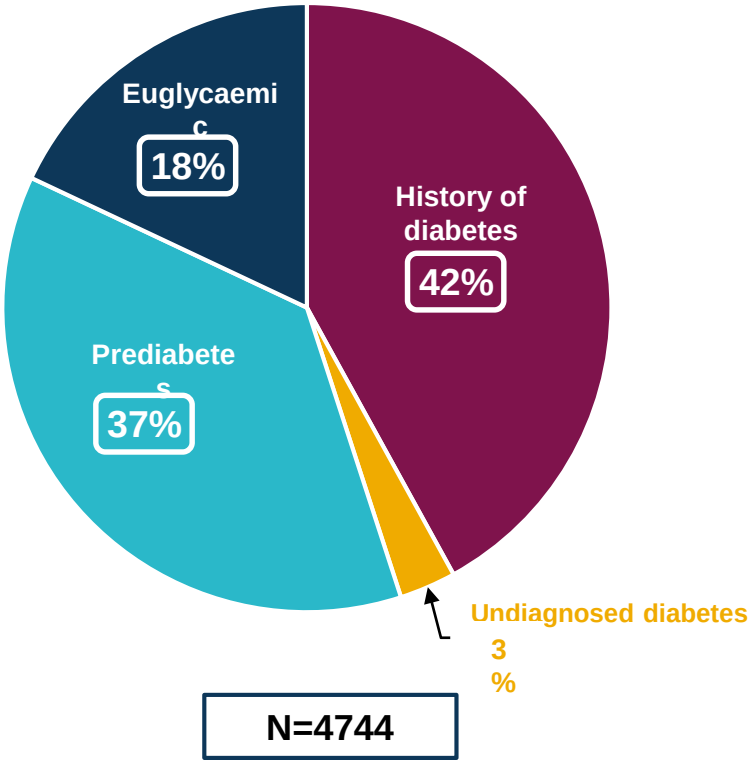
# Distribution of Patients by Glycaemic Status




**Euglycaemic (n=857)**

- HbA1c <5.7% at Visits 1 and 2

**History of diabetes (n=1983)**

- Provided by investigators

**Undiagnosed diabetes (n=154)**

- HbA1c ≥6.5% at Visits 1 and 2 in patients without diabetes history

**Prediabetes (n=1750)**

- HbA1c ≥5.7% at Visits 1 and 2 in patients without known or undiagnosed diabetes

HbA1c = glycated haemoglobin.

1. McMurray JJV et al. Article and supplementary appendix. *Eur J Heart Fail*. 2019;doi: 10.1002/ejhf.1548. Accessed July 16, 2019.



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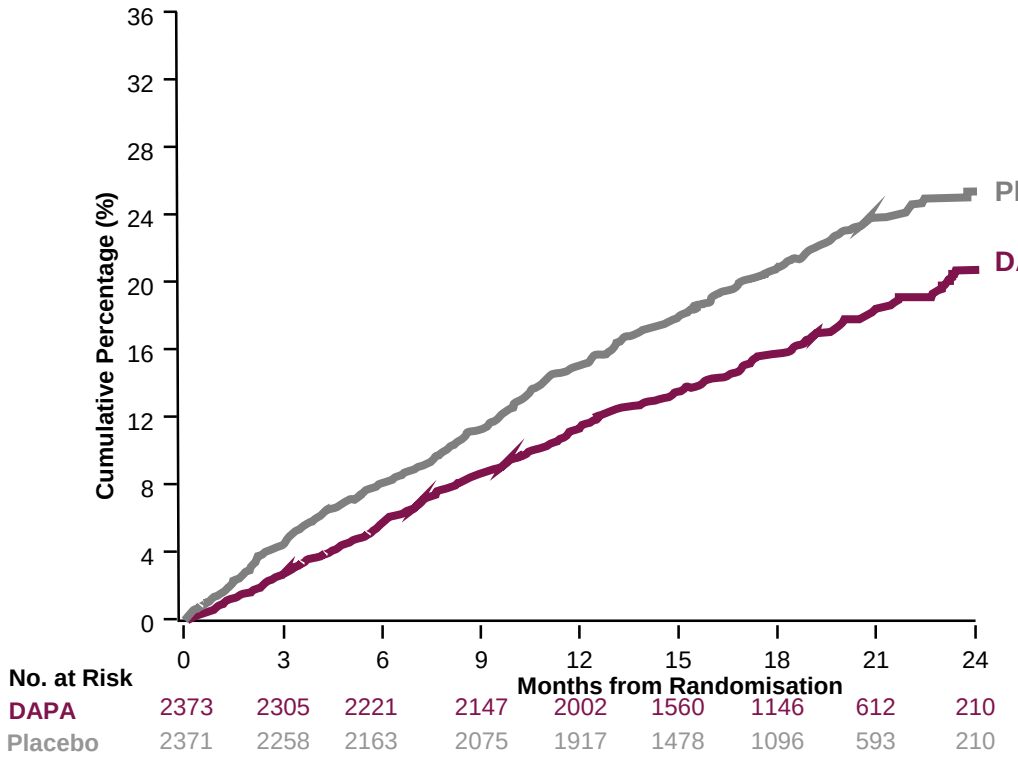
# Primary Endpoint: CV Death or hHF or an Urgent HF Visit[1]




**26% RRR**

**HR 0.74 (0.65, 0.85)**
**p=0.00001**

**NNT = 21**

Absolute Risk Reduction [ARR]=4% Event rate/100 patient years:
11.6 vs 15.6; p=0.00001

DAPA = dapagliflozin; HF = heart failure; hHF = hospitalisation for heart failure; HR = hazard ratio; NNT = number needed to treat.



1. McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France.

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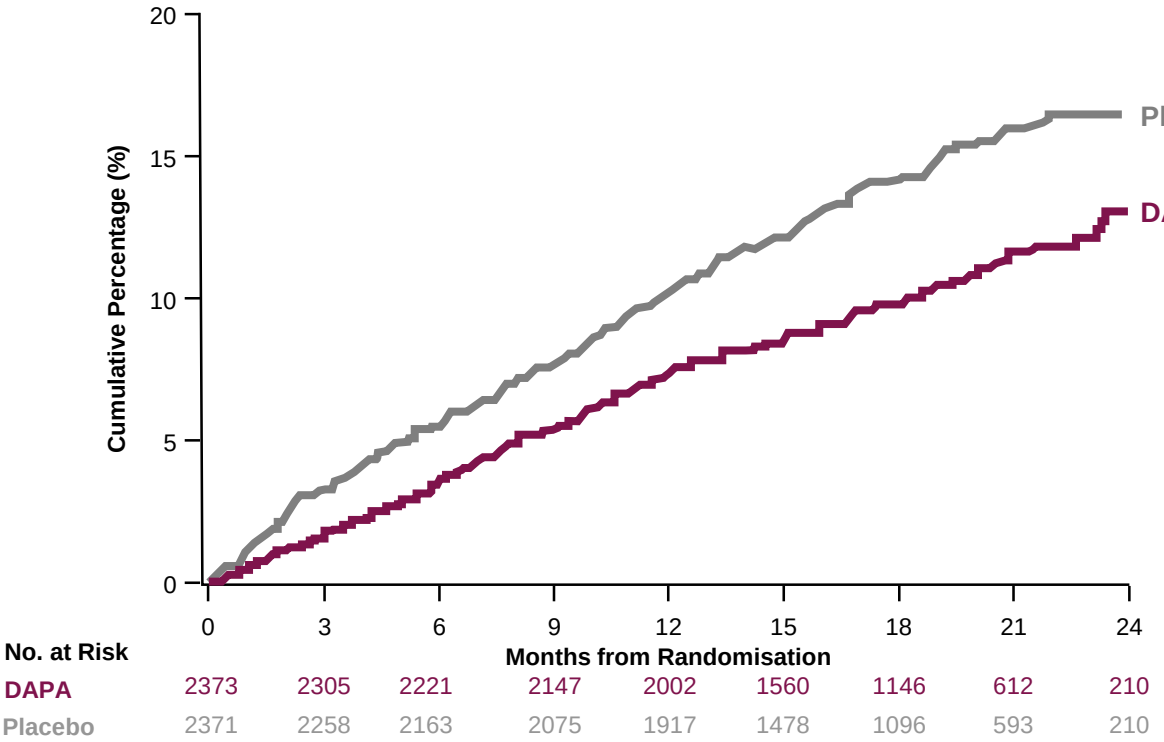
# Component of Primary Endpoint: Worsening HF Event




Absolute Risk Reduction [ARR]=3% Event rate/100 patient years:
7.1 vs 10.1; p=0.00003

DAPA = Dapagliflozin; HF = Heart failure; HR = Hazard ratio.



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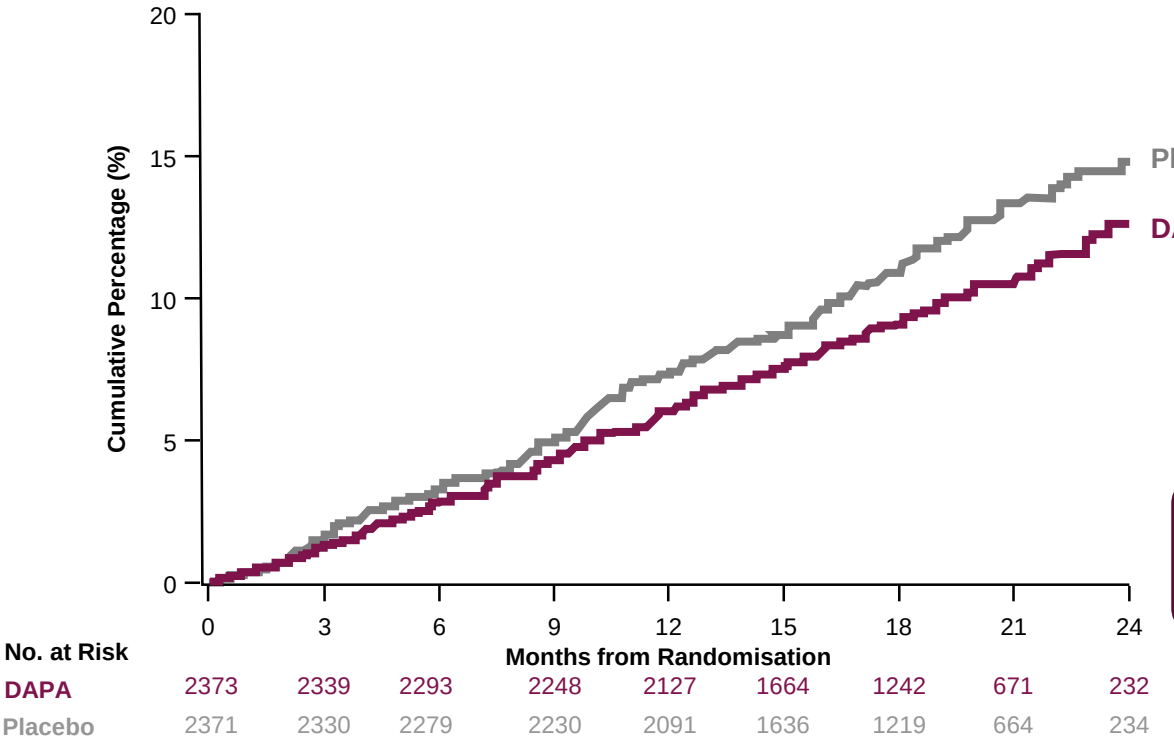
# Component of Primary Endpoint: Cardiovascular Death




Absolute Risk Reduction [ARR]=1.4%
Event rate/100 patient years: 6.5 vs 7.9; p=0.029

DAPA = Dapagliflozin; HR = Hazard ratio.



McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France.

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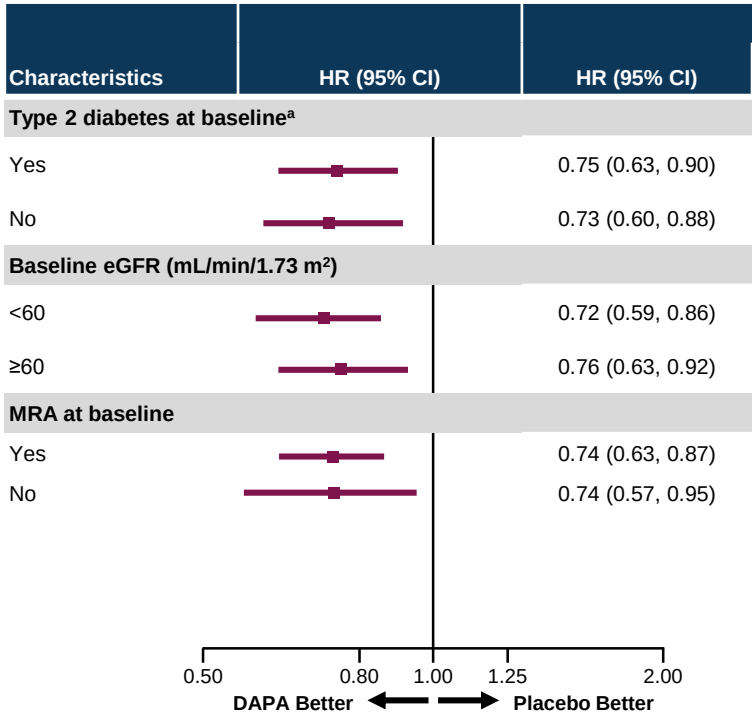
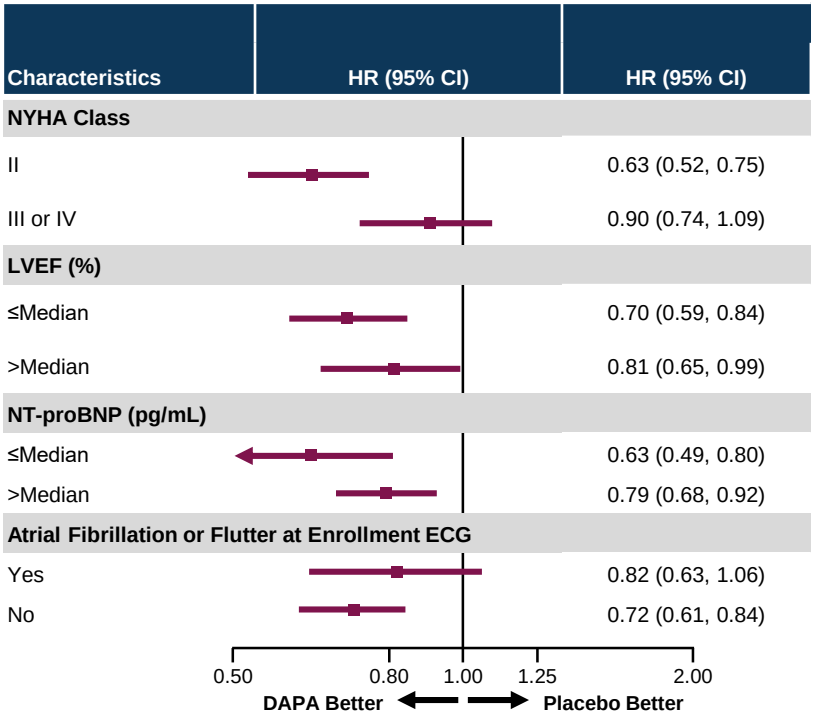
# Primary Endpoint: Prespecified Subgroups




A selection of subgroups is presented above.

[a]Defined as history of T2DM or HbA1c ≥6.5% at both enrollment and randomisation visits.

DAPA = dapagliflozin; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HR = hazard ratio; MRA = mineralocorticoid receptor antagonist; NT pro BNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction.

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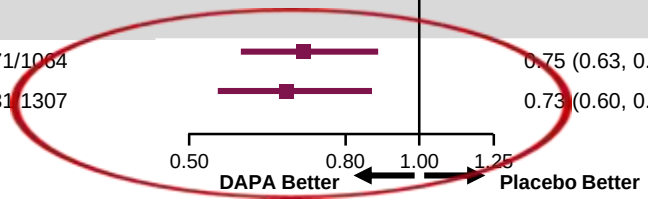
# Primary Endpoint: Subgroup Analyses

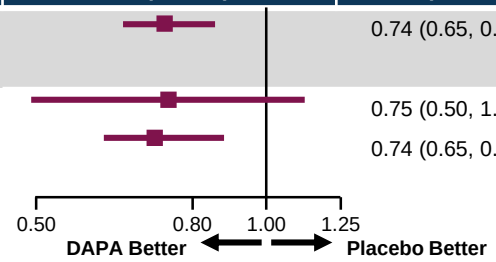
*Prespecified* Subgroup

| Characteristics | Dapagliflozin (n=2373) | Placebo (n=2371) | HR (95% CI) | HR (95% CI) |
|---|---|---|---|---|
| **All Patients** | 386/2373 | 502/2371 | | 0.74 (0.65, 0.85) |
| **Type 2 Diabetes at Baseline*** | | | | |
| Yes | 215/1075 | 271/1064 | | 0.75 (0.63, 0.90) |
| No | 171/1298 | 231/1307 | | 0.73 (0.60, 0.88) |




*Post-hoc* Subgroup

| Characteristics | Dapagliflozin (n=2373) | Placebo (n=2371) | HR (95% CI) | HR (95% CI) |
|---|---|---|---|---|
| **All Patients** | 386/2373 | 502/2371 | | 0.74 (0.65, 0.85) |
| **Angiotensin Receptor Neprilysin Inhibitor (ARNI)** | | | | |
| Yes | 41/250 | 56/258 | | 0.75 (0.50, 1.13) |
| No | 345/2123 | 446/2113 | | 0.74 (0.65, 0.86) |




*Defined as history of type 2 diabetes or HbA1c ≥6.5% at both enrollment and randomisation visits.



McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France.

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# Safety/Adverse Events

| Patients exposed to at least one dose of study drug | Dapagliflozin (n=2368) | Placebo (n=2368) | p-value |
|---|---|---|---|
| Adverse events (AE) of interest (%) | | | |
| Volume depletion[+] | 7.5 | 6.8 | 0.40 |
| Renal AE[‡] | 6.5 | 7.2 | 0.36 |
| Fracture | 2.1 | 2.1 | 1.00 |
| Amputation | 0.5 | 0.5 | 1.00 |
| Major hypoglycaemia | 0.2 | 0.2 | - |
| Diabetic ketoacidosis | 0.1 | 0.0 | - |
| AE leading to treatment discontinuation (%) | 4.7 | 4.9 | 0.79 |
| Any serious adverse event (incl. death) (%) | 38 | 42 | <0.01 |

[+]Volume depletion serious AEs in 29 dapagliflozin patients (1.2%) and 40 placebo patients (1.7%), p=0.23
[‡]Renal serious AEs in 38 dapagliflozin patients (1.6%) and 65 placebo patients (2.7%), p=0.009



McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France.

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# DAPA-HF Summary

- DAPA-HF is the first heart failure outcomes trial with an SGLT2 inhibitor investigating the treatment of HF in adults with HFrEF on top of standard of care (which includes medicines such as ACE-I, ARB, β-blockers, MRA, and ARNI) in patients with and without T2D.[1]
- Dapagliflozin provided a statistically-significant and clinically meaningful reduction in the risk of worsening heart failure events and cardiovascular death when compared to placebo, as well as improvement in heart failure symptoms, when added to standard therapy.[1,2]
- The safety findings of DAPA-HF were consistent with the well-established safety profile of dapagliflozin and the rate of discontinuation was low.[1,2]

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor-neprilysin Inhibitor; β-blockers = beta-blockers; CV = cardiovascular; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; SGLT2 = sodium-glucose cotransporter 2; T2D = type 2 diabetes.

1. AstraZeneca Pharmaceuticals LP press release. Published August 20,2019. 2. McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France.

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## SGLT2i guidelines :

***The UK improving Diabetes Steering committee***

**Open access article : Aimed at Primary Care**

Ali, A., Bain, S., Hicks, D. et al. Diabetes Ther (2019) 10: 1595. https://doi.org/10.1007/s13300-019-0657-8

**SGLT2 Inhibitors: Cardiovascular Benefits Beyond HbA1c – Translating Evidence into Practice**

**The Improving Diabetes Steering Committee: Ali A[1], Bain SC[2], Hicks D[3], Newland-Jones P[4], Patel DC[5], Evans M[6], Fernando K[7], James J[8], Milne N[9], Viljoen A[10], and Wilding J[11]**

Forxiga® (dapagliflozin) is indicated for the treatment of adults with insufficiently controlled Type 2 diabetes

Diabetes Professional Care - DPC | ABCD | AstraZeneca

# DECLAREING WAR ON THE BURDEN OF TYPE 2 DIABETES

**Date:** Tuesday 29th October 2019
**Venue:** Apex Room
**Address:** Olympia London
Hammersmith Road, Kensington, London W14 8UX

| | | |
|---|---|---|
| 18:00 | Arrivals and buffet | |
| 18:30 | Chairman's opening - **The battle in front of us** | *Prof Partha Kar, Portsmouth* |
| 18:45 | **The burden of heart failure in patients with Type 2 diabetes** | *Dr Dipesh Patel, London* |
| 19:25 | **Forxiga (dapagliflozin): Time to DECLARE New Evidence Beyond Glycaemic Control** | *Prof John Wilding, Liverpool* |
| 20:00 | **Value beyond glycaemic control DECLARE TIMI-58 Trial** | *Dr Marc Evans, Cardiff* |
| 20:20 | **Ask the experts** | |
| 20:45 | **Close** | |

**Register at: http://goto.az/dpcdeclare**

## FOR TODAY FOR TOMORROW


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